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Meta-Analysis

Meta-Analysis of the Role of Varenicline in Smoking Cessation

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ABSTRACT

Background: Smoking is the leading cause of premature death in both developed and developing countries. Smoking cessation efforts can be classified into pharmacological and therapeutic strategies. Varencline is the latest discovery for pharmacological therapy for smoking cessation programs. This study aims to determine the role of varenicline on smoking cessation efforts.
Subjects and Method: This was a systematic review and meta-analysis conducted using PRISMA flow diagrams. Search articles through journal databases including: Google Scholar, MEDLINE/ PubMed, Science Direct, Scopus, and Spinger Link by selecting articles published in 2011-2021. The keywords used are "varenicline" OR "pharmacotherapy" AND tobacco OR smoke OR smoked OR smoker AND "smoking cessation". The research instrument used to assess smoking cessation efforts was the Fagerstrom Test for Nicotine Dependence (FTND). The inclusion criteria were full paper articles with Randomized Controlled Trial (RCT) research methods, the relationship measure used was Mean SD, the intervention given was varenicline, the research subjects were adult smokers who wanted to quit smoking. Eligible articles were analyzed using the Revman 5.3 application.
Results: Meta-analysis of 9 articles showed results (SMD -0.11; 95% CI = -0.17 to -0.05; p<0.001).
Conclusion: Varenicline has a statistically significant effect in reducing the frequency of smoking per day.

Keywords: Varenicline, smoking cessation, quitting smoking

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BACKGROUND

Based on data from The Tobacco Atlas 6th Edition in 2018, the percentage of the world's population who consumes tobacco was 57% from Asia and Australia, 14% in the population of Eastern Europe and the Soviet Union, 12% in the American population, 9% in the population Western Europe, and 8% in the population of the Middle East and Africa. Meanwhile, ASEAN is a region with 10% of smokers in the world and 20% of the causes of death are caused by consuming tobacco. The percentage of smokers in ASEAN countries themselves are Indonesia (46.16%), the Philippines (16.62%), Vietnam (14.11%), Myanmar (8.73%), Thailand (7.74%), Malaysia (2.90%), Cambodia (2.07%), Laos (1.23%), Singapore (0.39%), and Brunei (0.04%) (Drope et al., 2018).

According to a report by the World Health Organization (WHO), smoking is a significant factor causing cardiovascular and respiratory diseases and more than 20 different types or subtypes of cancer. More than 8 million people die from tobacco use each year, and most of these deaths occur in low-

and middle-income countries. Tobacco use is not only harmful to smokers themselves, but passive smoking also affects non-smokers. According to WHO statistics, 1.2 million deaths each year are related to exposure to secondhand smoke. The impact of smoking, or secondhand smoke, on pregnant women and children should be considered. Every year, 65,000 children die from diseases related to secondhand smoke. Smoking during pregnancy can also cause lifelong health problems. Therefore, various countries and organizations are trying to find effective ways to help people who depend on tobacco quit smoking (Guo et al., 2021).

Smoking habits are not new for Indonesian teenagers, especially for high school students. In this adolescent period, adolescents have complex problems, especially in the awareness of healthy behavior. An increase in unhealthy behavior such as tobacco consumption is still commonly found in today's youth (Rapiudin, 2015). Previous studies reported that important factors that contribute to the increased risk of smoking among adolescents include peer pressure through smoking siblings and/or friends, tobacco industry advertisements and easy access to tobacco products and their low prices (Arifianti et al., 2019).

Currently, there are many types of filter cigarettes and non-filter cigarettes circulating that include a 'low tar' label on the packaging. The American Federal Trade Commission (FTC) states that cigarettes with a low-tar label do not determine how much tar content enters the body when a cigarette is smoked. This is because the amount of tar that enters the body is also influenced by how smokers smoke their cigarettes, whether they are inhaled deeply or shallowly.

Conventional cigarettes are the most widely consumed types of cigarettes in the community. Conventional cigarette smoke is known to contain approximately 4000 types of hazardous chemicals, including carbon monoxide, nitrogen oxides, nitrosamines, nitrospirolidin, formaldehyde, pyridine, benzopyrine, nickel, arsenic, nicotine, phenol and tar. These substances are known to be harmful substances that can injure lung tissue (Putra et al., 2019).

Tobacco use is the leading preventable cause of death in the United States and the world. Although rates of smoking initiation in adolescence have declined in the past decade, most adult smokers start smoking before the age of 21, and nearly all adolescents who smoke regularly will continue to smoke into adulthood, leading to a life expectancy of at least 10 years shorter than non-smokers. smoker. Nearly two-thirds of adolescent smokers are interested in quitting, but only 4% to 6% of unaided quit attempts are successful (Gray et al., 2019).

Within 20 minutes of quitting smoking, heart rate increases and blood pressure decreases. After 12 hours, the level of carbon monoxide in the blood decreases. Within 2-12 weeks, blood circulation increases and lung function improves. After 1-9 months, cough and shortness of breath are reduced (WHO, 2020). Individuals who try to quit smoking will experience physical symptoms such as depression, frequent anger, frustration, insomnia, difficulty concentrating, anxiety, increased appetite, decreased heart rate, and a desire to smoke. These symptoms will appear intensely within 2-48 hours after quitting smoking and usually decrease significantly within 2-4 weeks. Smoking cessation efforts can be classified into pharmacological and therapeutic strategies. Pharmacological strategies use nicotine replacement therapy, and non-nicotine replacement therapies such as

varenicline, bupropion, and nortriptyline (Alexandridi et al., 2018).

Among the existing pharmacological therapies are divided into three major groups, namely nicotine replacement therapy (NRT), bupropion and varencline. Varencline is the latest discovery for pharmacological therapy for smoking cessation programs. In general, pharmacotherapy to stop smoking can be divided into two, namely first-line and second-line. Some drugs that are included in the first line are: bupropion and varenicline. Bupropion is an antidepressant that acts as an inhibitor of dopamine and norepinephrine reuptake. Varenicline is a partial agonist of the nicotine receptor. These drugs, if used properly, will increase the success rate of smoking cessation efforts (Wiratmoko et al., 2017).

Many primary studies have investigated the effect of varenicline on smoking cessation efforts. Further analysis is needed to reach a convincing conclusion. Based on this background, researchers are interested in conducting a systematic review and meta-analysis on "Effect of varenicline on smoking cessation efforts".

SUBJECTS AND METHOD

1. Study Design

This a systematic review and meta-analysis study design. Using the PRISMA flow chart guidelines. Article searches were carried out using journal databases including: PubMed, science Direct, Google Scholar and Spinger-Link articles in the 2010-2020 range with the keywords “varenicline” OR “pharmacotherapy” AND tobacco OR smoke OR smoked OR smoker AND “smoking cessation”.

2. Inclusion Criteria

This study has inclusion criteria, including: Full paper article with a Randomized Controlled Trial (RCT) study design, articles published in Indonesian and English, the size of the relationship used with Mean SD, The intervention given is varenicline, study subjects adult smokers who want to quit smoking.

3. Exclusion Criteria

This study has exclusion criteria, including: research subjects < 18 years old, articles published in languages other than English, articles not full text, articles before 2011.

4. Operational Definition of Variables

The formulation of the research problem was carried out by considering the eligibility criteria defined using the PICO, namely, Population: active adult smokers 18 years, Intervention: varenicline, Comparison: placebo, and Outcome: smoking cessation. Varenicline is a non-nicotine pharmacological treatment option approved by the Food and Drug Administration (FDA) for smoking cessation (Vogeler et al., 2016).

The success of smoking cessation is the success of adult smokers on nicotine replacement therapy. The success of quitting smoking is influenced by the frequency of smoking and the intention to quit smoking (Rosita, 2012).

5. Instrument

The instrument in this study is the Fagerstrom Test for Nicotine Dependence (FTND) to assess the frequency of smoking per day.

6. Data Analysis

Data analysis in this study was carried out using the Review Manager application (RevMan 5.3). Data were analyzed based on variations between studies by determining the use of random effects analysis models. In this study I^2 was used to quantify the dispersion. The results of data analysis are in the form of the effect size value of the heterogeneity of the study which later the results of the data that have been analyzed are interpreted in the form of forest plots and funnel plots.

RESULTS

Research from the primary study related to the role of varenicline on smoking cessation efforts contained 9 articles with a total sample of 4386 participants, 2260 participants for the intervention and 2126 participants for comparison.

Articles were obtained from 3 continents, namely, 7 studies from the North American continent, 1 study from the Asian continent and 1 study from the Australian continent. Each study had a sample of more than 100 participants. Outcome for some articles mentions an increase in attempts to quit smoking after being given varenicline.

The article search was carried out using a database based on the PRISMA flow diagram, which can be seen in Figure 1. The study quality assessment was carried out qualitatively and quantitatively. Assessment of research quality using the Critical Appraisal Skills Program (CASP) can be seen in Table 1. Each of the 11 questions was answered with the answer choices: Yes, No and Unclear. After assessing the quality of the study, 9 articles that were included in the quantitative synthesis process of the meta-analysis were analyzed using RevMan 5.3.

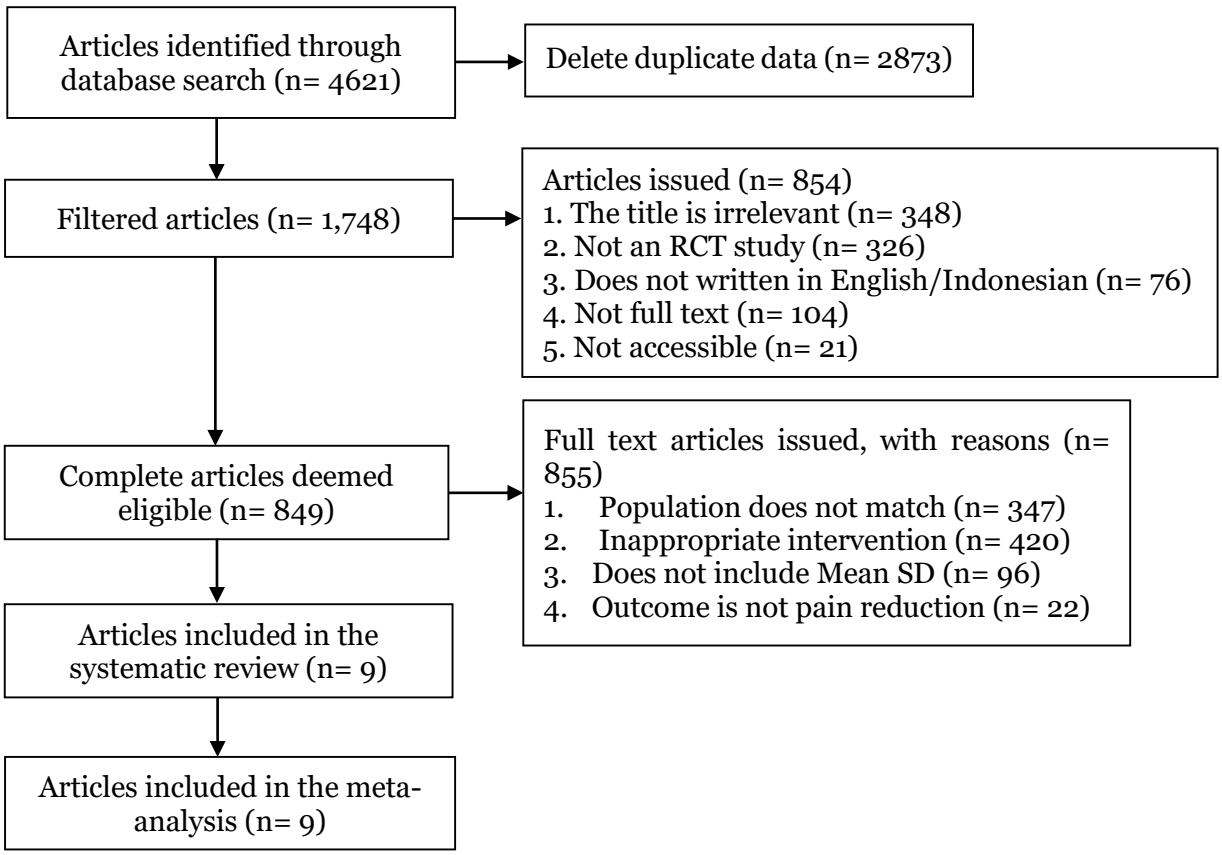

Figure 1. PRISMA flow diagram

Table 1. Assessment of Research Quality on the Role of Varenicline in Quitting Smoking Efforts

No.	Question	Baker et al (2016)	Bohadana et al (2020)	Carson et al (2020)	Cinciripini et al (2018)	Ebbert et al (2015)	Lerman et al (2015)	Schnoll et al (2019)	Stein et al (2013)	Wong et al (2016)
1.	Does the experiment answer the clinical problem clearly?	1	1	1	1	1	1	1	1	1
2.	Was the intervention given to the patient randomized?	1	1	1	1	1	1	1	1	1
3.	Are there blinding of patients, health workers, and researchers?	1	1	1	1	1	1	1	1	1
4.	Were the study groups similar at the start of the study?	1	1	1	1	1	1	1	1	1
5.	Outside of the intervention under study, were the study groups treated equally?	1	1	1	1	1	1	1	1	1
6.	Were all patients included in the study properly accounted for in the conclusions? were all patients analyzed according to the randomized study groups?	1	1	1	0	1	1	1	1	0
7.	Is the effect of the intervention large enough?	1	1	1	1	1	1	1	1	1
8.	How precise is the estimation of the effect of the intervention?	1	1	1	1	1	1	1	1	1
9.	Are the results applicable to the context of practice or local populations?	1	1	1	1	1	1	1	1	1
10.	Are all other clinically important outcomes considered in this article?	1	1	0	1	0	0	1	0	1
11.	Do the benefits provided by the intervention outweigh the costs and disadvantages?	1	1	1	1	0	1	1	1	1

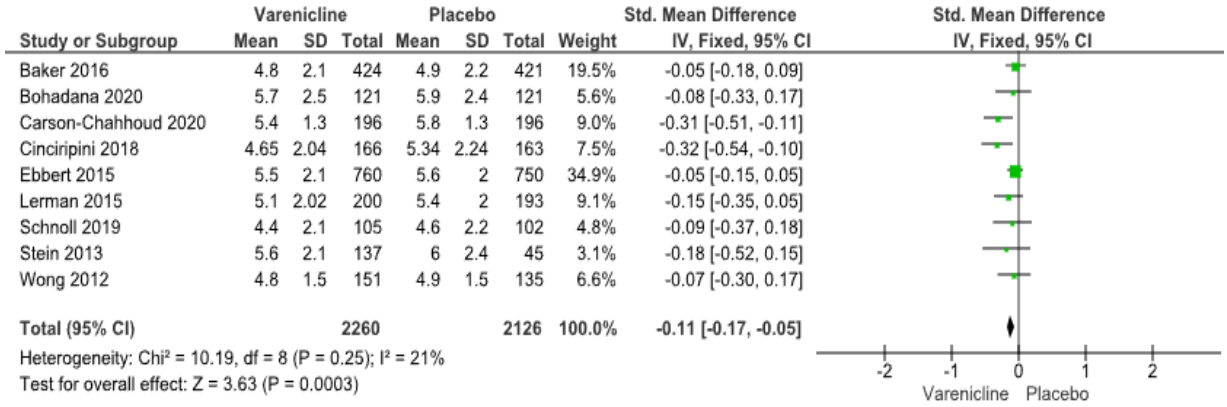

Figure 2. Forest plot of varenicline on smoking cessation efforts

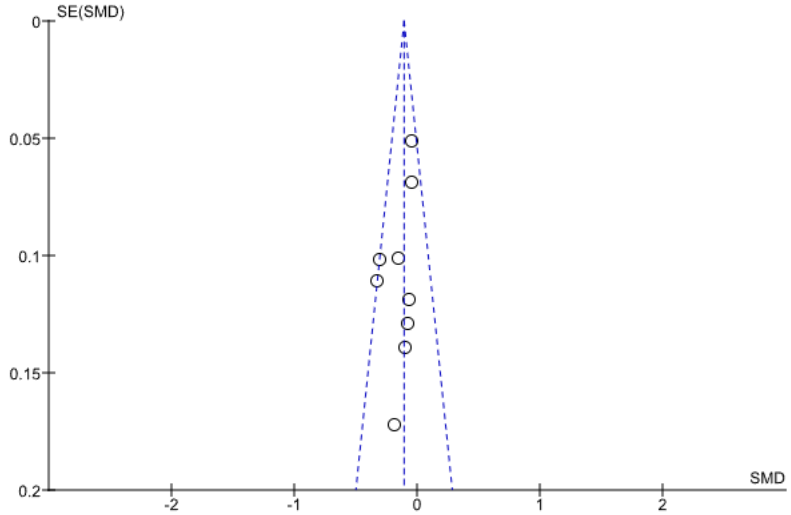

Figure 3. Funnel plot of varenicline on smoking cessation efforts

DISCUSSION

1. The role of varenicline in smoking cessation efforts

a. Forest plot of varenicline on smoking cessation efforts

Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 2 shows as many as 9 articles reporting that administration of varenicline therapy can reduce the frequency of smoking per day compared to being given a placebo.

The heterogeneity of the research data shows I^2= 21% so that the distribution of the data is declared homogeneous (fixed effect model). The results of the analysis of the varinecline intervention found that -0.11 times reduced the frequency of smoking per day compared to placebo, and was statistically significant (SMD -0.11; 95% CI= -0.17 to -0.05; p<0.001).

b. Funnel plot of varenicline on smoking cessation efforts

A funnel plot is a plot that represents the approximate size of the effect of each study on the estimate of its accuracy which is usually the standard error. Figure 3 funnel plot varenicline shows no publication bias as indicated by the symmetrical right and left plots where 4 plots are on the right and 5 plots are on the left. The plot on the left of the graph has a standard error between 0.05

and 0.15 and the plot on the right has a standard error between 0.1 and 0.2. The absence of bias can also be seen from the balance between the distances between studies on the right and left sides of the funnel plot.

Varenicline is a non-nicotine pharmacological treatment option approved by the Food and Drug Administration (FDA) for smoking cessation. Varenicline acts as a partial agonist at nicotinic 4β2 receptors. Its efficacy in smoking cessation is thought to be due to its high affinity and selective binding to these receptors, simultaneously preventing nicotine binding. Vogeler et al (2016). The US Public Health Service has included varenicline as first-line therapy in the 2008 smoking cessation guidelines along with NRT and bupropion. Varenicline can be a treatment option for patients who have never received pharmacotherapy at all or for those who have failed other pharmacotherapy.

In this systematic review, there are 9 articles of intervention studies identified worldwide from 2011 to 2021. This study analyzes articles using the Mean SD measure. The results of the systematic review and meta-analysis are presented in the form of forest plots and funnel plots. A forest plot is a diagram that shows an overview of the information from each of the studies examined in the meta-analysis and estimates of the overall results (Murti, 2018). The forest plot also shows visually the magnitude of variation (heterogeneity) between study results. The funnel plot shows the relationship between the effect size of the study and the sample size or standard error of the effect size of the various studies studied (Murti, 2018). The possibility of publication bias in the funnel plot can be seen from the asymmetry of the number of studies on the right and left sides.

In the primary study used in this study, the Fagerstrom Test for Nicotine Dependence (FTND) was used to measure the level of nicotine dependence that had been given to varenicline therapy in research subjects. Where the subjects of this study are active smokers aged 18 years and over who used to have the desire to quit smoking and are willing to quit smoking.

The forest plot results of 9 research articles in the RCT design showed that adult smokers taking varenicline reduced the frequency of smoking per day by -0.11 times compared to adult smokers given placebo, and were statistically significant (SMD -0.11; 95% CI = -0.17 to -0.05; $p<0.001$).

This study is in line with Bohadana et al (2020), that using varenicline during the first 6 weeks of smoking cessation efforts effectively reduces the frequency of smoking rates per day. Therefore, the data in this study support the view that the use of varenicline 6 weeks before treatment should be extended to enhance the effect of the drug. This trial also supports the idea that the varenicline intervention would be more effective in reducing cigarette consumption if administered for 12 consecutive weeks.

Based on a study by Huang et al (2012), varenicline therapy compared with placebo was associated with a beneficial effect on decreased cigarette consumption at the end of 52 weeks. However, the disadvantage is the psychiatric events associated with the administration of varenicline therapy. This should be further studied with larger and quality studies, and people with mental illness should be given special treatment with varenicline therapy.

The results of this study are in line with Jordan and Xi (2018), showing that the development of varenicline was based on strong theoretical reasons and preclinical evidence. Clinical studies show that vareni-

cline is safe and more effective in maintaining abstinence than placebo, bupropion or nicotine replacement therapy. However, given that rates of continuous abstinence throughout the study remained low (18~30% with varenicline; 4~10% with placebo), new and more effective drugs targeting other nicotinic or glutamate receptors for smoking cessation are needed.

This is in line with Gunawan (2012) that the pharmacokinetic properties of varenicline do not produce serious side effects and significant drug interactions. However, monitoring of this drug still needs to be done. So far, the administration of varenicline for up to 12 months has been declared safe from serious side effects. Evidence from clinical trials suggests varenicline is superior to placebo, bupropion and NRT. However, further studies are needed to prove and establish the clinical efficacy of varenicline.

Various attempts to quit smoking are contained in guidelines that have been developed by experts. The first thing to do is awareness and intention of smokers to quit smoking, given support, pharmacology such as varenicline and regular follow-up. A study conducted by Zhao et al. (2020) stated that there was a significant relationship between TPB and smoking intention in Austrian smokers, namely according to the theory of planned behavior smoking behavior is determined by intention and perceived behavioral control. Intention in turn is influenced by subjective attitudes and norms.

This statement is in line with Islami et al (2019) which shows that intention has a significant effect on smoking behavior in adolescents. Adolescents with weak intention had 3.85 units lower than those with strong intentions to smoke. Intention to smoke in adolescents is caused by several external factors, namely the presence of friends or family who smoke. This finding is supported by the theory of planned behavior (TPB) which states that behavior is determined by behavioral control and intention to become a behavior. Intention is influenced by attitude, subjective norm, and individual behavioral control, the three components interact with each other and become a determinant of the formation of intentions that are carried out or not carried out.

Based on this, support for smokers to quit smoking is very necessary with efforts to support smokers so that they have the intention to stop smoking and seek health promotion by increasing smokers' knowledge about the dangers of smoking and ways to quit smoking. This is important because varenicline is a therapeutic option that has the potential to be applied to the treatment of smoking addiction among smokers. The goal is that the number of Indonesian smokers can decrease. Thus, the demographic bonus for Indonesia which is expected to occur in 2035 is able to produce healthy and quality human resources.

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This study is self-funded.

AUTHORS CONTRIBUTION

Muhammad Zainul Lafif is the main author who selects the topic, searches and collects research data. Bhisma Murti and Hanung Prasetya analyzed data and reviewed research documents.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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