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COMPARISON OF VARENICLINE'S EFFECTIVENESS WITH NICOTIN REPLACEMENT THERAPY (NRT) OR A COMBINATION OF BOTH IN SMOKING CESSATION: LITERATURE REVIEW

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ABSTRACT

Smoking is a cause of many chronic diseases such as lung cancer, oral cancer, to cardiovascular disease. Smoking addiction is caused by the nicotine in cigarettes. Thus Nicotine Replacement Therapy (NRT) was created as a substitute for nicotine consumption without smoking. While another drug that is widely prescribed is varenicline. However, varenicline is not yet available in Indonesia and the use of NRT is still very rare. Therefore, research is needed to compare the efficacy of the two. The research was conducted by studying the literature of international journals and obtained 12 journals that match the research title. As a result, varenicline monotherapy proved to be more effective than NRT or a combination of both.

1. INTRODUCTION

Smoking is one of the causes of many non-communicable diseases such as heart disease, cancer, and pregnancy disorders. Smoking itself has been classified as an epidemic because it can kill up to 8 million people every year. In 2020, there are about 22.3% of the total world population smoking, with details of 36.7% of the total male population and 7.8% of the total female population. Smoking has also been shown to reduce the life expectancy of active smokers in the age range of 35-69 years. Based on a study conducted in the UK, 90% of patients diagnosed with lung cancer are caused by smoking. [1] Nicotine in cigarettes can cause physiological changes by affecting the nervous system through the lungs. Nicotine will bind to the cholinergic acetylcholine receptors which are responsible for the release of neurotransmitters such as dopamine, and others resulted in changes in mood or behavior, producing pleasure, and stimulation. If exposure to nicotine occurs in the long term, there will be changes in neurons at the cellular and molecular levels and end in tolerance, sensitization, to dependence. [2]

To date, there are many therapeutic options for cigarette addicts. Some of them are Varenicline and Bupropion. Varenicline acts as a partial agonist of the nicotine receptor. Varenicline itself has been considered superior to Bupropion. [3] In addition, there is also a therapy group called Nicotine Replacement Therapy (NRT). Most of the toxins in cigarettes come from other substances such as carbon monoxide, but nicotine is the substance responsible for cigarette addiction itself. Thus, NRT was created to reduce the motivation to smoke with various nicotine delivery systems. Among them are through transdermal patches, nicotine gum, inhalers, lozenges, and others. [4]

In Indonesia alone, research on the effectiveness of varenicline and NRT is still very limited. For this reason, it is necessary to conduct a literature study based on several research journals abroad regarding the efficacy of Varenicline and NRT. In this study, the efficacy of varenicline monotherapy will be compared with NRT, the combination of multiple NRTs, and the combination of varenicline with NRT.

2. METHOD

The literature study was carried out using an article search method on Google Scholar, ScienceDirect, and PubMed, with the keywords 'varenicline', 'nicotine replacement therapy', 'smoking

cessation', and 'efficacy' between 2012-2022. The results obtained 12 articles relevant to the research title.

3. RESULTS AND DISCUSSION

Based on the results of the literature study, there were 12 articles that matched the title of the study. From the results of each journal, we can conclude that most studies show that varenicline has a better effectiveness than NRT, except in the study of Baker et al., 2016, which stated that the effectiveness of Varenicline is comparable to the effectiveness of monotherapy with one NRT or a combination of NRT, also on therapy. Chang et al., 2019, who stated that varenicline has an equivalent effectiveness to NRT in the category of patients >55 years

Table 1. Results of Literature Study Efficacy of Varenicline with various combination therapies or monotherapy.

Research	Types of Research	Description	Result
Hajek et al., 2013	Randomized Controlled Trial	There's a possibility for type II error.	VR > VR + NTP
Baker et al., 2021	Randomized Controlled Trial	The study also compared the duration of therapy.	VR > VR + NTP
Ramon et al., 2014	Randomized Controlled Trial	Patients analyzed by subgroup.	VR > VR + NTP
Baker et al., 2016	Randomized Controlled Trial	An open-label study	VR = NTP = cNRT
Taylor et al., 2017	Prospective Cohort Study	The length of study was 4 years.	VR > NRT
Hsueh et al., 2021	Prospective Cohort Study	The length of study was 1 year.	VR > NRT
Gray et al., 2015	Randomized Controlled Trial	In female patients	VR > NTP
Jimenez-Ruiz et al., 2018	Studi Kohort Retrospektif	Patients with mental health disorders	VR > NTP
Kotz et al., 2014	Prospective Cohort Study	In adult patients. The length of study was 6 months	VR > NRT
Chang et al., 2019	Prospective Cohort Study	The study was conducted in two age categories, patients aged 25-54 years and patients aged >55 years. The length of study was 6 months.	VR > NRT in patients aged 25-54 years VR = NRT in patients >55 years old
Hsueh et al., 2014	Prospective Cohort Study	The length of study was 3 years.	VR > NTP
Hsueh et al., 2014	Randomized Controlled Trial	In adolescent patient (14-21 years)	VR = Placebo during weekly therapy. VR > Placebo at the end of therapy

VR: Varenicline, NRT: Nicotine Replacement Therapy, NTP: Nicotine Transdermal Patch

Varenicline was first developed by Pfizer company in 1997 and received approval from the Food Drug Association (FDA) in 2006. The development was based on the compound cytisine, a compound also known as one of smoking cessation therapies. [5] This literature study concluded that varenicline is superior to NRT either as a combination therapy with NRT or as a single therapy. Of the 12 journals reviewed, 6 of them conducted research using the randomized controlled trial method. A randomized controlled trial is an experimental, comparative, and quantitative research conducted under controlled

conditions but with a random allocation of the intervention to a control group. This study is popular in the health sector because it can provide accurate data on the cause-and-effect relationship between interventions and outcomes which can then be used as evidence-based practice. [6]

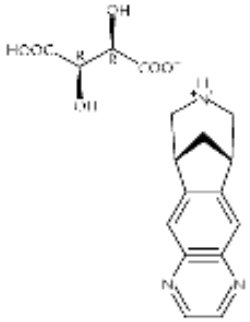

Figure 1. Structure of Varenicline

3 of 6 randomized controlled trials compared the efficacy of varenicline monotherapy with the combination therapy of varenicline and nicotine transdermal patch (NTP) or nicotine patches. As a result, the combination of varenicline and nicotine patches was shown to not increase the efficacy of varenicline, and varenicline monotherapy was shown to be more effective at week 12. [7], [8] This is in line with the study of Baker et al., 2021 who conducted an abstinence test at week 52, the result was that there was no significant difference between varenicline monotherapy with a combination of varenicline and nicotine patches.[9] In a randomized controlled trial, patients will be examined with several variables, namely the level of exhaled carbon monoxide, the number of cigarettes consumed since the last counseling, as well as the number of cigarettes consumed since the start of therapy. Later the patient's abstinence will also be calculated. Abstinence is a condition where the patient does not consume cigarettes at all, and also does not consider smoking or consuming nicotine in any form. [10]In addition, another variable studied was also the length of therapy. There was no significant difference in the results of the abstinence test between patients who were given 12 weeks of therapy and those who were given 24 weeks of therapy.

This is different from a study conducted by Baker et al., 2016 which compared the efficacy of varenicline, nicotine patches, and a combination of NRT. The study showed that there was no significant difference in patients carbon monoxide levels between one therapy and another. Another thing to note from this study is that the study was conducted in an open label trial where both the researcher and the patient knew information about the drugs given or consumed. [11] It is different with the three studies previously mentioned where the study was conducted in a blinded manner, where both the researcher and the patient did not know what drug information was given and consumed to avoid bias in research. [12]

Gray et al., 2019 conducted a study that tested the efficacy of varenicline by comparing its efficacy with placeboA placebo is a substance that are made so similar to the drug to be tested for efficacy, which aims to prove the effectiveness of the drug without being influenced by psychological and patient beliefs. [13] Based on the results of the study, there was no significant difference in the primary outcome between patients taking varenicline or placebo when the challenge test was performed. However, when secondary examination found that varenicline can provide a better long-term effect. [14]

In addition to randomized controlled trials, another method used is cohort studies. A cohort study is a study in which researchers will follow a population for a certain period of time to determine the effect of a drug. [15] Cohort studies in assessing the effectiveness of varenicline have several limitations, including that patients can choose what therapy they want to receive, so there is a possibility for the results to be biased. In addition, this study was also conducted by contacting patients via telephone calls at certain times to determine the patient's abstention condition, without carrying out biochemical tests (urine tests, carbon monoxide levels, etc.) on the patient. [16]

Among the 6 cohort studies, 5 of them were prospective cohort studies, where the researcher was present at the time of exposure (in this case the prescription of therapy) and routinely monitored patients for a certain period of time. The cohort study was conducted over a period of 6 months [17], [18] 1 year [16], 3 years [19], and 4 years [20].

4 of 5 prospective cohort studies were conducted, comparing the effectiveness of varenicline with NRT therapy in achieving abstention. Chang et al., 2019 & Kotz et al., 2014 both conducted a cohort study 6 months apart, Kotz et al. in his study stated that varenicline users were patients with a younger age than those who chose NRT, and the result was that varenicline was more effective in helping patients achieve abstention conditions. This is in line with the research conducted by Chang et al. who suggested that varenicline was effective in patients aged 25-54 years, while in those in the 55 year age category, there was no significant difference between NRT and varenicline in helping patients achieve abstention. [17], [18] Another cohort study conducted by Hsueh et al. in 2021 at a clinic in Taiwan with a period of 1 year. This study states that varenicline is better at helping to quit smoking than NRT at week 52. Another finding is that the success of therapy is also related to several factors such as male gender, having a higher income, and lower nicotine dependence. [16]

Taylor et al., in a 2017 study examined the effectiveness of varenicline compared to NRT in primary health facilities, so from here we can assess the effectiveness of varenicline in patients whose economic conditions are in the middle-low category. The results showed that varenicline proved to be more effective as a smoking cessation therapy than NRT. It can also be concluded from this study that the socioeconomic conditions of the patients did not change the effectiveness of varenicline. [20]

A similar study was also conducted by Hsueh et al. in 2014 with differences comparing the effectiveness of varenicline with nicotine patches. This follow-up study was conducted 3 years after the first therapy. As a result, varenicline resulted in a higher abstention rate for up to 3 years than the nicotine patch. [19] The only retrospective cohort study was conducted by Jimenez-Ruiz et al. in 2018. The study was conducted at one of the Quitting Smoking clinics in Madrid with a special category, namely patients with mental disorders. The medical records studied were medical records between 2009-2016. The results showed that varenicline and NRT were proven safe as smoking cessation therapy in patients with psychiatric disorders, with varenicline having a higher abstention rate than NRT. [21]

4. CONCLUSION

Varenicline is more effective in helping patients who want to quit smoking than Nicotine Replacement Therapy (NRT). Its effectiveness as monotherapy is also higher than when combined with NRT. Further research is expected to conduct clinical trials of varenicline in Indonesia because varenicline has proven its efficacy in helping patients quit smoking. This is also supported by the fact that WHO has given permission for varenicline to be used as smoking cessation therapy.

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