

SYSTEMATIC REVIEW

A Systematic Review on Effectiveness of Nicotine-Based and Non-Nicotine Based Drug Delivery System for Smoking Cessation Among the Elderly

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ABSTRACT

Introduction: Smoking is associated with a higher risk of mortality, especially in smokers with cardiovascular and respiratory diseases. Smoking cessation remains the most effective approach in reducing smoking-related illness risks at all ages. For elderly smokers, smoking cessation has been proved to prolong life expectancy and reduce the risk of stroke and ischemic heart disease. However, a wide selection of smoking cessation medications makes prescribing challenging, especially among elderly smokers. Inability to recommend the best treatment may reduce the smoking cessation success rate in the elderly. Therefore, this study compares the effectiveness of pharmacotherapy available and correlate the effect of ageing on the effectiveness, leading to the recommendation of the best medication for elderly smokers. **Method:** A systematic searching strategy was performed in three different databases by using pre-determined search strings. **Results:** Overall, this systematic review revealed that varenicline showed the greatest smoking cessation rate among the elderly, followed by bupropion and NRT. **Conclusion:** It is suggested that varenicline offered the best medical aid for smoking cessation in the elderly.

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INTRODUCTION

Smoking significantly affects morbidity and mortality in recent years. Tobacco use accounted for 7.69 million deaths and 200 million disability-adjusted life-years worldwide in 2019 (1). This shows a significant health issue that needs to be catered to. Globally, 21.2% of the world population with age more than 15 years are reported smoking in developing countries. This showed that almost one of three parts of the world population is associated with smoking. A prevalence of 17.1% is reported in the American adult's population (2). However, these numbers vary among different countries, wherein in Malaysia, about 21% and 5% of the Malaysian population were reported to smoke cigarette and e-cigarette, respectively (3).

Generally, smokers are susceptible to have smoking-associated diseases, namely cancer, cardiovascular disease (4), respiratory disease, impaired immune

function and inflammation (5). These diseases may contribute to a person's high mortality and morbidity rate, especially during the occurrence of pandemic Covid-19. Besides that, a higher percentage of Covid-19 infected smokers were reported needing ICU support, mechanical ventilation, and severe cases. Based on the data, smokers were 1.4 times more likely to have severe symptoms of Covid-19 and 2.4 times more likely to be admitted to ICU (6). This indicates an alarming issue for smokers, especially older age. This is because the elderly have more tendency to get infected into more severe cases due to their lower immune defence and associated co-morbidities. Therefore, older smokers are suggested to stop smoking and initiate a pharmacological intervention for smoking cessation. Selecting the pharmacotherapy intervention is solely based on its effectiveness, safety and individual preference.

Nicotine replacement therapy (NRT), bupropion and varenicline are commonly used in managing tobacco use and dependence (6). Varenicline and bupropion are drugs that affect dopamine release in the brain and can block nicotinic receptors. In contrast, nicotine replacement treatments, such as gum, tablet, or patch, can deliver nicotine at a lower amount than cigarettes.

With the guidance of Clinical Practice Guideline (CPG) on Treatment of Tobacco Use and Dependence 2003 by the Ministry of Health, health care providers may counsel the smokers on the convenient smoking cessation services available in Malaysia. In addition, even the elderly are recommended to start smoking cessation due to the proven benefits of smoking cessation, including lowering the risk of morbidity and mortality, increasing average life span by up to 3.7 years and lowering the risk of coronary heart disease and stroke (8). Therefore, physicians should urge older smokers to quit and play a vital role in the smoking cessation process.

However, a wide selection of smoking cessation medications available cause difficulties in individualized prescription among the elderly. As far as this concern, there is a lack of studies that compare the effectiveness of available pharmacotherapy treatment in older smokers. Because of that, this review aims to provide insights into the effectiveness, advantages and safety of nicotine-based and non-nicotine-based drug delivery systems for smoking cessation in the elderly. This review paper can be a guide to recommend the best pharmaceutical products for smoking cessation in the elderly to enhance its success rate.

In this review, the authors recommend the best intervention for the elderly to quit smoking. This can be a guide to the pharmacist to dispense proper treatment based on individual preferences. As there is still a lack of research, the authors gathered the relevant articles to observe the effectiveness and safety of the available treatments to treat this nicotine dependence, specifically in the elderly. Due to advanced age, the elderly may have several co-morbidities that may affect the effectiveness of the therapy. Moreover, some of the interventions may produce several adverse effects that lead to poor compliance. Therefore, this review is used as an approach to provide the best therapy for the elderly for smoking cessation.

METHODS

In this part, the method used is selecting related articles regarding nicotine-based and non-nicotine-based delivery systems for smoking cessation in elderly. The reviewers used the PRISMA method, which includes databases namely Scopus, ProQuest and Pubmed to carry out a systematic review that included identifications, screening, eligibility, quality appraisal and data abstraction and analysis.

The review protocol – PRISMA

This systematic review is guided by the PRISMA statement.

Formulation of the research question

This systematic review was formulated using PICO. PICO is a tool that allows the authors to come up with

a relevant research question for the review. The main elements in PICO namely Problem, Interest, and Context. Therefore, the authors have three primary aspects in the review based on this concept namely smoking cessation among elderly (Problem), nicotine-based and non-nicotine-based (Interest) and drug delivery system (Context) which further assist the authors to define the key research question: what is the best smoking cessation medications for elderly?

Systematic searching strategies

There are three main processes in the systematic searching strategies namely identification, screening, and eligibility.

Identification

The process of identification of keywords, followed by the process of searching for the synonyms of the keywords was carried out. Search string namely ((nicotine OR “nicotine replacement therapy”) AND (bupropion OR bupropion OR varenicline OR nortriptyline) AND (smok* OR “smoking cessation” OR tobacco) AND (elder* OR ageing OR older) AND (gum* OR transdermal* OR patch* OR oral* OR sublingual* OR spray* OR inhaler*)) was developed. The search string was conducted on three databases namely Scopus, ProQuest and PubMed with records acquired are 84, 2000 and 22 articles, respectively. Meanwhile, a search string namely “nicotine replacement therapy OR varenicline OR bupropion OR nortriptyline OR smoking cessation OR combination therapy AND elderly” was developed and conducted on clinicaltrials.gov. The records achieved are 1875 clinical trials.

Screening

The articles were screened automatically by using the sorting function available in the databases. It was carried out using the study’s inclusion and exclusion criteria, which are shown in Table I below. As a result, a total of 3140 articles were eliminated based on the exclusion criteria. Following next, the authors proceeded on screening the title of the articles. 13 duplicated articles were detected and excluded from the study. The final step in this process was abstract screening. Two authors, NAA and NHMS were responsible to perform the screening. Any disagreement was resolved by third person, ANMH. At the end of screening process, a total of 828 articles were accepted for eligibility process.

Table I: Inclusion criteria for this systematic review

Criteria	Inclusion
Literature Type	Original research article, clinical trials
Language	English
Timeline	2021-2017
Nature of the study	Focus on the use of nicotine based, non-nicotine based and combination therapy for smoking cessation among elderly.

Eligibility

Three authors ANMH, NAA and NHMS were responsible in reviewing each of the retrieved articles to ensure they meet all of the requirements. This part was accomplished by reading the articles thoroughly. A total of 828 articles were reviewed for eligibility with 781 articles were excluded due to a lack of information regarding nicotine-based and non-nicotine-based delivery system for smoking cessation in elderly. As a result, 47 articles left proceeded to the quality appraisal step.

Quality Appraisal

Quality appraisal was performed to guarantee the content of the article was of high quality. 47 articles were examined independently and were ranked as high, medium and low quality based on the predetermined criteria. The criteria were developed based on the constructed research question of this systematic review. Axis tool was used as the guide to construct the criteria. A mutual agreement was practised among the authors to eliminate bias. For this research, the authors only included high and medium quality articles for this study. Thus, a total of 18 articles proceeded with data abstraction and analysis. There are various criteria that the article must meet in order for the author to choose it. For example, the publication must be a research paper or a clinical trial with English as the primary language. The article will be rejected if it focuses on other populations rather than smoking cessation therapy for the elderly or on the economic evaluation. Aside from that, the article will be rejected if all three authors agree that it is of low quality. Fig. 1 shows the flow chart of the searching strategy.

Data abstraction and analysis

The data in this research were analysed using a qualitative methodology. The data abstraction was done in response to the constructed research questions. The summary of each article was summarised into advantages and disadvantages of the treatment available for smoking cessation in elderly. Table II shows a summary of the studies that were included.

Clinical trial

In this section, randomised clinical trial was also used as a search engine in this review. The related articles regarding nicotine-based and non-nicotine-based delivery system for smoking cessation in elderly were searched in the clinicalTrial.gov website. Four clinical studies were found to be related to this review. Thus, the authors used these clinical studies as evidence to support the findings.

RESULTS AND DISCUSSION

The selection of smoking cessation pharmacotherapies depends on patient preference and response, especially for the elderly. In this review, the available treatments for smoking cessation are divided into three main groups:

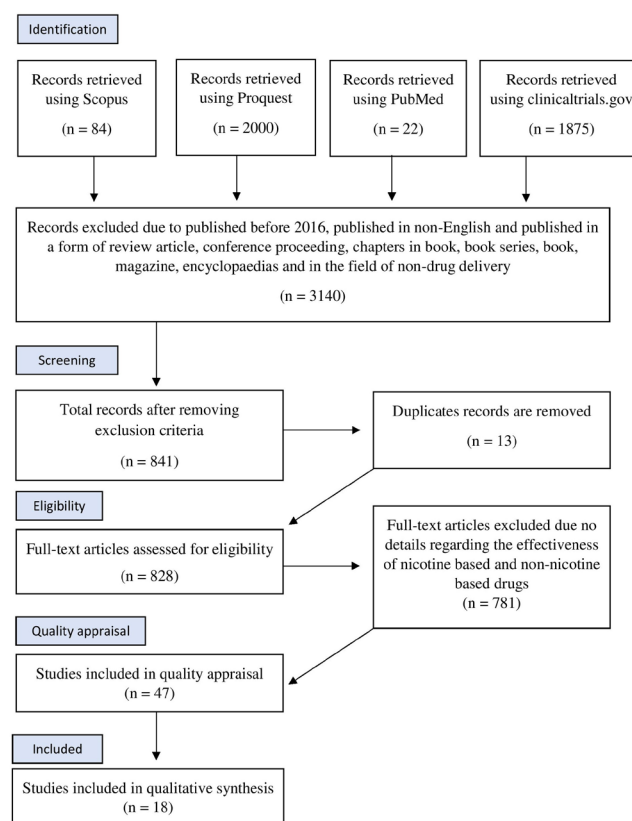


Figure 1: Flow chart of the searching strategy

nicotine-based drugs, non-nicotine-based drugs and combination therapy. The nicotine-based drug includes nicotine gum, patch, lozenges and inhaler. These NRTs are available as over-the-counter drugs, which means they do not require any prescription. The non-nicotine-based drug including bupropion, varenicline and nortriptyline, and the combination therapy were also discussed in this review.

Nicotine-based drug/ Nicotine replacement therapy

Nicotine gum

Nicotine gum is widely used as a first-line pharmacotherapy option to assist smoking cessation and remains the most popular among other established NRTs. The use of nicotine gum is widely available as it does not require a prescription (9). However, in Malaysia, nicotine gum is only available in two strengths, either 2 mg or 4 mg (10). Two brands were registered under National Pharmacy Regulatory Agency (NPR), namely Nicotine icy mint and Quitt ® Peppermint. Nicorette icy mint is marketed in both strengths, while Quitt ® Peppermint nicotine gum is only available in 2 mg.

Nicotine dose appears to be a key element in determining the efficacy of NRT for the treatment of tobacco dependence. In practice, smokers may not take enough doses of oral NRT per day to achieve maximal benefit. The underdosing issue has been identified as a factor that results in suboptimal treatment effects. A new gum containing 6 mg nicotine was developed to provide

Table II: Summary of included studies

Year	References	Quality Appraisal			Drug	Advantages	Disadvantages
		ANMH	NAA	NHMS			
2018	(7)	High	High	High	Nicotine gum	Higher abstinence rate with NRT combine with behavioural treatment.	-
2017	(8)	Medium	High	Medium	Nicotine patch	Additional reduction in cigarettes smoked per day.	-
2017	(8)	Medium	High	Medium	Varenicline	Promote the reduction in smoking rate, cravings, and dependence.	-
2020	(9)	Medium	High	Medium	Nicotine patch	Affordable and easy to access	-
2020	(9)	Medium	High	Medium	Combination of nicotine patch and gum	Higher cost-effectiveness.	-
2019	(11)	Medium	High	Medium	Nicotine lozenges	-	Combination of nicotine lozenges with other NRT increase the frequency of side effect such as indigestion, hiccups, nausea, and mouth irritation.
2019	(11)	Medium	High	Medium	Combination of nicotine patch and lozenges	-	Significantly induced side effect with this combination.
2019	(12)	Medium	High	High	Nicotine patch	-	Higher risk of having skin adverse effect in the elderly.
2019	(12)	Medium	High	High	Varenicline	More effective compared to NRT.	-
2018	(13)	Medium	High	Medium	Nicotine patch	No significant increase in cardiovascular events.	-
2018	(13)	Medium	High	Medium	Varenicline	More effective compared to NRT.	Associated with higher risk of cardiovascular events. Increased risk of neuropsychiatric adverse events among those 65 years or older.
2020	(16)	High	High	High	Varenicline	Increase quit attempt with the use of varenicline for 4 weeks. More effective compared to NRT.	-
2017	(18)	Medium	High	Medium	Varenicline	Not associated with neuropsychiatric events.	-
2017	(18)	Medium	High	Medium	Bupropion	Decrease risk of cardiovascular events and neuropsychiatric adverse events among smokers with COPD compared to NRT.	-
2017	(18)	Medium	High	Medium	Combination of bupropion and varenicline	-	Does not show any significant improvement compared to varenicline monotherapy
2019	(19)	Medium	High	Medium	Nortriptyline	Suppress the negative effect of quitting smoking.	-
2020	(20)	High	High	Medium	Combination of Varenicline and NRT	Optimise tobacco abstinence rates for more than 64 weeks. Higher abstinence rate with the use of this combination compared to varenicline monotherapy.	-
2020	(21)	High	High	Medium	Nicotine patch and lozenge	Higher abstinence rate and mean reduction in cigarettes per day.	-
2020	(22)	High	High	High	Varenicline and nicotine patch	Higher abstinence rate with varenicline-only treatment in standard duration.	Lower abstinence rate for the combination therapy in standard duration.

an extra dosing alternative for heavily dependent smokers or those who require enhanced craving relief. One randomized clinical trial study revealed that the reduction in smoking cravings was more significant with 6 mg compared to 4 mg nicotine gum in the first 1 and 3 hours after administration. With 6 mg nicotine gum, a 50% reduction in perceived impulses to smoke was achieved in 9.4 minutes compared to 16.2 minutes with 4 mg nicotine gum (11). Thus, the study proved that 6 mg of nicotine gum provided rapid and more extended relief of urges and reduced the desire to smoke more effectively than 4 mg of nicotine gum.

Apart from the underdosing issue, researchers were also interested in finding how age factors may influence nicotine gum's effectiveness in smoking cessation. A study conducted found that the use of nicotine gum as a monotherapy agent was more effective in promoting cessation in older age compared with the younger age. It has been hypothesized that pharmacokinetics, mainly metabolism rate, contributes to different effectiveness of NRT observed in older groups (11). Based on the findings, it is suggested that nicotine gum work effectively as NRT, especially among elderly smokers, since it helps in reducing craving through chewing action. This subsequently increases the success rate of smoking cessation from 36%, which is observed in the combination of varenicline and bupropion, to 45.9% using nicotine gum alone. Another randomized controlled trial study found that smokers who received enhanced care (Nicorette Gum/Nicoderm CQ, Behavioral Smoking Cessation Counseling and Smoking Quitline Referral) completed the treatment slightly more than the participants receiving standard care (Nicorette Gum/Nicoderm CQ and Smoking Quitline Referral only). Out of 134 participants who enrolled on the program, 96 of them managed to abstain from smoking (13). This indicates that smoking cessation counselling also may contribute to improving the outcomes of nicotine gum for smoking cessation.

Generally, nicotine gum as nicotine replacement therapy is widely being practised to reduce withdrawal feelings and cigarette cravings. It helps in reducing withdrawal symptoms by releasing a small amount of nicotine which satisfies the craving and subsequently reduces the urge to smoke. All included studies for nicotine gum also support the evidence that gum is safe and effective to be used as one of quit smoking medications. This suggested that nicotine gum as first-line therapy in aiding smoking cessation among elderly smokers is recommended. Elderly smokers who are heavily dependent may require higher strength of nicotine gum to be more effective.

Nicotine patch

In recent years, nicotine patches have commonly been used in smoking cessation. It is one of the preferable pharmacotherapies in managing the nicotine craving among smokers. Nicorette Invisi Transdermal Patch is an

example of a brand found in Malaysia, which is available in three strengths, namely 10mg/16 hours, 15mg/16 hours, and 25mg/16 hours. A study was conducted to determine its effectiveness, where nicotine patch has been used as a pre-quit patch regimen. This is mainly because pre-quit nicotine patches reduce smoking satisfaction, and in turn, it drives to smoking cessation. It is proven when the active group treated with a pre-quit patch showed an additional reduction in cigarettes smoked per day (14). In addition to that, this patch is affordable and easy to access as an over-the-counter medication. Transdermal patches were also associated with abstinence rates of approximately 18% lower than the varenicline, which shows lower effectiveness of nicotine patches compared to varenicline (15). These may be due to the decrease in transdermal nicotine patch absorption in the elderly due to reducing blood perfusion in skin tissue.

Compared with another form of nicotine replacement therapy, the average user of the nicotine patch has only a 20-25% chance of achieving long-term abstinence and increased in smokers with greater adherence (16). Adherence to the patch treatment is essential in achieving long-term cessation as it can manage nicotine cravings. Moreover, a study was conducted to observe the successful rate of nicotine patches compared to varenicline and NRT combination of lozenge and patch in smoking cessation. It is found that nicotine patch therapy is given a higher abstinence rate compared to varenicline and NRT combination due to its high adherence (17). In terms of safety and side effects, nicotine patches may cause adverse skin events in the elderly (18). Also, no significant increase in the neuropsychiatric or cardiovascular event was found using nicotine patch compared to varenicline (19).

Therefore, nicotine patch use is recommended to be used as first-line therapy due to its high abstinence rate, affordability, ease to access and produce long abstinence period. Even so, nicotine patches may need a higher dose due to their low absorption in the elderly. The main reason for lower absorption in the elderly is reducing blood perfusion in skin tissue, especially those with co-morbidities. It also has a high tendency skin adverse effect, namely skin irritation which may produce poor adherence. Nevertheless, this patch can still be used as first-line therapy in smoking cessation due to its cost-effectiveness, efficacy and low risk of an adverse event in the elderly. Furthermore, all the studies mentioned above discussed the effectiveness and side effects of using a nicotine patch in the elderly, thus they are considered high quality articles.

Nicotine lozenges

Nicotine lozenges were the least choice to assist smoking cessation (15,18). In Malaysia, NiQuitin 2 mg and 4 mg Mint Lozenges are the products that were registered. Smokers who are sensitive to nicotine lozenges' side

effects were most likely to find it too challenging. An example of lozenge side effects is indigestion, hiccups, nausea, and mouth irritation. This effect occurs more frequently if the smokers combine nicotine lozenges with other NRT (15,20). More studies are needed to conclude the effectiveness of nicotine lozenges in older smokers. The outcomes of the study were not fully discussed, and more studies are needed to conclude the effectiveness of nicotine lozenges in older smokers.

Nicotine inhaler

The nicotine inhaler is the least commonly used in smoking cessation, especially among the elderly. This inhaler is usually marketed as Nicotrol and Nicorette Inhaler (Pfizer) but is only available overseas. It benefits by mimicking the stimulation of hand-to-mouth smoking cigarettes. This type of drug delivery provides the most direct access to the target area without requiring a high dose. This is mainly because of the wide surface area, blood supply and fine epithelial layer that cause a high absorption rate. It is a very convenient and non-invasive way of delivering nicotine (21). However, it needs frequent puffing and may cause mouth and throat irritation. Therefore, the use of inhaled nicotine in the elderly is not recommended to be administered as it may produce poor compliance. Nonetheless, more research on nicotine inhalers in smoking cessation for the elderly is needed, as the studies' findings show only a few benefits.

Non-nicotine-based drug

Varenicline

The use of antidepressants for smoking cessation is also widely being practised in clinical settings. Varenicline, widely known as Champix, is marketed in two strengths: either a 0.5 mg or 1 mg film-coated tablet. It is a partial agonist of nicotinic receptors, which promoted the reduction in the smoking rate, cravings and dependence (13). A randomized controlled trial was conducted to compare the quit attempts between the varenicline and control groups. Out of 50 participants who received a sample of varenicline for four weeks, 26 of them managed to make a 24-hour quit attempt. Meanwhile, only 17 out of 49 participants made a 24-hour quit attempt for the control group. This proved that the using varenicline alone could increase the quit attempt among smokers (22).

In term of effectiveness comparison, some studies found that varenicline is more effective in aiding smoking cessation than NRT (16,17). A prospective cohort study found that patients with varenicline prescriptions were more likely to be abstinent up to 4 years than patients who took NRTs (23). Skin adverse effects and dental problems due to the use of NRT may contribute to a higher prescription of varenicline among elderly smokers. Furthermore, because they had more underlying comorbidities treated with oral drugs, the

senior group preferred more for oral medication. In contrast, a study proved that varenicline did not offer greater effectiveness in cessation among elderly smokers than NRT (8). Except for the type of medication used, there is no significant difference found among baseline characteristics such as gender, nicotine dependence, and the presence of underlying disease in determining smoking cessation success (2,16).

In terms of safety, varenicline appears to be correlated with a higher risk of cardiovascular events. Higher incidence risks can be observed among those under and over 65 years old, regardless of a history of cardiovascular events or not (19). These findings indicated that varenicline could increase cardiovascular risk regardless of age, gender, or medical history of the users. Generally, the use of varenicline does not appear to be associated with neuropsychiatric events such as mood or anxiety disorders (24). However, a study found that varenicline users aged 65 years or above had significantly associated with a higher risk of neuropsychiatric adverse events (19). This finding was presumably due to increased sensitivity of varenicline effects among the elderly. In contrast, another study found that varenicline and bupropion were unlikely to increase the risk of cardiovascular and neuropsychiatric adverse events among smokers with COPD (24).

Overall, the included studies had sufficiently provided the evidence on the effectiveness of varenicline in smoking cessation. In addition, the included studies also discussed on the adverse effects of varenicline particularly for older population which justified the high-quality appraisal credited by the authors. In practice, varenicline is widely being prescribed as first-line therapy for cessation aid among smokers. As for the elderly, although there is no conclusive data regarding the safety issue of varenicline, the medication is still recommended as it had been scientifically proven to be effective in aiding smoking cessation. However, concerns on the use of varenicline, especially in terms of safety, should also be addressed. Further studies are required to validate these results in a larger and more representative sample.

Bupropion

Bupropion sold under the brand name Wellbutrin is classified as anti-depression and prescribed as a smoking cessation agent to smokers. As smokers age, they present with multiple diseases that could be caused by chronic smoking. For example, the older chronic smokers present with Chronic Obstructive Pulmonary Disease (COPD), cardiovascular disease (CVD), and hypertension before using NRT, bupropion or varenicline to assist in smoking cessation. However, bupropion was less popular compared to NRT and varenicline in all group ages (16). One of the factors that cause the smokers to choose NRT or varenicline over bupropion was because they believe that bupropion or varenicline could cause

serious adverse effects for smokers with co-morbidities. According to the study, smokers with COPD or CVD that take bupropion or varenicline has been reported to have fewer side effects compared to NRT although NRT is the most popularly used (24). Therefore, it is recommended for older smokers with co-morbidities to switch to bupropion or varenicline to stop smoking. All in all, the studies have provided the proofs on the effectiveness and benefits of bupropion as the smoking cessation treatment for older population.

Nortriptyline

Nortriptyline classified under the tricyclic antidepressant class is generally used as a second-line pharmacotherapy option for smoking cessation. As evaluated by the profile-of-mood-state total mood disturbance score (POMS-TMD) during the first eight days of quitting smoking, nortriptyline suppressed the negative effect of quitting smoking on the body. In addition, it is also shown to optimise tobacco abstinence rates for more than 64 weeks, as predicted by the extent of negative mood during early nicotine withdrawal symptoms (25). The outcomes of the study were not fully discussed, but the study was still included in this paper as it mentions a few advantages on the use of nortriptyline. However, the use of this agent is limited probably due to its potential side effects such as dry mouth, sedation, and constipation. In addition, as the database for nortriptyline is not extensively available, issues on potential adverse events and concerns on overdose should be considered first before initiating the treatment. Therefore, it is suggested to reserve nortriptyline as second-line therapy for cessation aid among elderly smokers.

Combination therapy

Several researchers found that using a combination of different smoking cessation pharmacotherapies can increase abstinence rates. Other than that, the individual cost per life was higher when using the combination therapy of nicotine patch and gum. However, it is still considered cost-effective as it is even available in low-resource countries such as Jordan (15). In another study, it is found that a combination of varenicline and NRT exhibits a higher continuous abstinence rate compared to varenicline monotherapy (26). In contrast, the addition of bupropion to varenicline does not show any significant improvement compared to varenicline monotherapy (16). Another nicotine therapy combination is the combination of nicotine patch and lozenge. This combination reduced adherence without increasing abstinence when compared to varenicline. However, it is reported that the combination NRT significantly induced the side effect of lozenges such as ingestion, hiccups or mouth problems compared to nicotine patch monotherapy (17).

A clinical study on smoking cessation using a combination of nicotine patches and nicotine lozenge was completed on patients diagnosed with mental illness.

The intervention group was given nicotine combination therapy and medical counselling, while the control group only received medical counselling. The outcome measures of this study are 7-day point prevalence abstinence and smoking reduction. The result showed that 26.3% and 21.1% of the participants achieve 7-day point prevalence abstinence in the intervention group, whereas 15.8% and 26.3% in the control group for the time frame of 8 weeks and six months after baseline. This showed a higher number of participants able to achieve smoking cessation using this combination of nicotine therapy. While for the smoking reduction, there is lower usage of cigarettes per day in the intervention group with a higher percentage of reduction (7.04%) compared to the control group (4.15%) in 8 weeks post-baseline. This can conclude the effectiveness of nicotine patches and nicotine lozenges combination therapy (27).

Next, a clinical trial was conducted to observe the effectiveness of varenicline and nicotine patches in combination therapy compared to varenicline treatment only. The addition of nicotine patches in the varenicline treatment exhibits slightly lower abstinence in participants compared with the other group. The intervention using varenicline only exhibits a slightly higher percentage (25.1%) in participants that confirmed to be complete abstinence from any cigarette use compared to the combination therapy (23.6%). In contrast, the use of combination therapy demonstrated a slightly higher abstinence rate (25.1%) in extended duration (addition of 24 weeks) compared to the varenicline-only therapy (24.4%). This showed that the use of combination does not show any significant improvement compared to varenicline monotherapy. However, the risk of itchiness and skin rash increased with varenicline and nicotine patch combination therapy with 13.11% and 17.38% compared to monotherapy with 3.0% and 11.33%. This adverse effect may significantly affect the adherence that leads to poor compliance. Overall, varenicline and nicotine patch use did not show any significant improvement compared to the varenicline only therapy in both duration due to lack of significant differences in the percentage of abstinence rate (28).

Based on these findings, the best combination therapy may be a nicotine patch and lozenge due to its high abstinence rate based on the clinical evidence. Nevertheless, it may produce poor adherence due to the induced side effect, namely ingestion and hiccups. Therefore, it is recommended to use a combination of nicotine patches and gum in terms of cost-effectiveness. On the other hand, the combination of nicotine patch and varenicline is not recommended due to the higher risk of adverse effects, namely skin rash and itchiness, that may significantly affect patient compliance. The outcomes of these high-quality studies demonstrated the efficacy and benefits of available combination therapy as the smoking cessation treatment for older population. However, further research needs to be done in the

elderly, especially on cardiovascular effects with the use of this combination.

Recommendation of smoking cessation mediation for elderly smokers

Patient compliance is one of the primary key factors that may influence the clinical outcome of smoking cessation therapy. As an approach to increase patient compliance, age may be used as a predictor in designing more individualized treatments for smokers. Based on data from the systematic review and randomized clinical trial studies, nicotine replacement therapy which includes nicotine gum or nicotine gum monotherapy, may be recommended as the first-line therapy for smoking cessation among the elderly. Apart from nicotine replacement therapy, varenicline also can be recommended as the first-line agent for elderly smokers. On the other hand, bupropion monotherapy was classified as second-line therapy for the elderly. Although the evidence was not very supportive, combination therapy was also recommended as second-line therapy in aiding cessation. The recommendations were made by considering two main factors which are the effectiveness and safety of the treatments.

Nicotine gum is recommended as the first-line agent for smoking cessation because it has proven to be effective and safe for elderly smokers. It works by reducing the withdrawal symptoms and cigarette cravings through the action of chewing (12). As a suggestion, heavily dependent smokers may also consider using a higher dose, such as 6 mg of nicotine gum. A higher strength of nicotine gum may provide a rapid and more extended craving relief which subsequently can increase smoking cessation success, especially in elderly patients (11). Besides that, the nicotine patch may also be recommended as first-line therapy as it gives an additional reduction of smoking per day as claimed by some studies (14, 17). However, the low absorption of nicotine patches among the elderly may become a concern. Due to aging factors, the blood perfusion in skin tissue became lowered, subsequently reducing the therapy's effectiveness as the absorption became reduced (15). A higher dose may be required to encounter the problem. In addition, it also has a high tendency to cause adverse skin effects, namely skin irritation that led to poor adherence (18). However, the nicotine patch is still categorized as first-line therapy in smoking cessation mainly due to its effectiveness and low risk of an adverse event in the elderly.

Unfortunately, some smokers were reported to experience some adverse skin effects and dental problems due to the use of nicotine patch and nicotine gum (23). As a solution, varenicline was suggested as another first-line therapy for smoking cessation among the elderly. Varenicline works by interfering with the receptors in the brain that are stimulated by nicotine. Data collected had proved that varenicline is superior in terms of

effectiveness as it results in a higher abstinence rate than nicotine-based therapy (16,17). However, some studies found that the use of varenicline is associated with cardiovascular and neuropsychiatric risk, presumably due to increased sensitivity of varenicline (19). Despite that, the use of varenicline as a medication aid in smoking cessation is continuously being practised. It is proved to be effective in decreasing the desire to smoke and alleviating the withdrawal symptoms. Thus, it is suggested that varenicline offered the best medical aid for smoking cessation in the elderly.

Bupropion monotherapy is recommended as the second-line therapy in aiding smoking cessation because it shows less significant side effects, especially when the smoker presents with COPD or CVD (24). Minor side effects can be translated to a higher adherence rate as the smoker often non-comply due to intolerable side effects. As a result, the duration of abstinence from tobacco is longer and possibly quit smoking. Some studies also had proven that dual treatments given to smokers can contribute to a higher abstinence rate. For example, a higher abstinence rate is observed with the combination of varenicline and nicotine replacement therapy (26). However, the combination of nicotine patch and varenicline exhibits a higher risk of adverse effects, namely skin rash and itchiness. This is due to nicotine patches as an adjuvant that leads to poor adherence and low patients' compliance (28). Hence, the combination therapy is the least recommended in elderly smoking cessation treatment. Nevertheless, further research needs to be done in the elderly, especially on cardiovascular effects and other adverse effects with the use of these combinations.

CONCLUSION

Overall, this systematic review revealed that varenicline monotherapy showed the most remarkable smoking cessation rate among the elderly, followed by bupropion and NRT. Using age as a predictor may offer a better approach in designing more individualized prescriptions, leading to an increase in success rates of smoking cessation. Other baseline characteristics, including gender, nicotine dependence and medical history, may not influence the effectiveness and success rate of cessation among the older group. Thus, it is suggested that varenicline offered the best medical aid for smoking cessation in the elderly.

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