International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Nicotine Inhaler and/or Bupropion for Smoking Cessation: A Randomized Comparative Study

Mohamed Nemr Othman[*1], *Heba Ahmed Salem*[2]

[1]*Psychiatry Department, Faculty of Medicine, Aswan University, Aswan, Egypt*

[2]*Chest Department, Faculty of Medicine, Tanta University, Tanta, Egypt*

Abstract

Various approaches are employed for treating smoking dependence, involving both non-pharmacological as well as pharmacological treatments. To compare nicotine inhaler and/or bupropion on smoking cessation when given alone or in combination. This prospective randomized comparative study involved 90 smokers aged from 18 to 65 years old, both sexes, smoking at least ten cigarettes daily for one year. The participants divided equally into three groups: Group N: received sixteen cartridges of nicotine inhaler daily. Group B: received bupropion 150 mg a day one before their intended quit date then 150 mg two times each day for two to eight weeks. Group NB: received both nicotine inhaler as well as bupropion. The overall Fagerström score in group N was 5.3 ± 2.94, group B was 5.2 ± 2.92, and in group NB was 5.7 ± 2.9 with insignificantly varance among all groups. Prevalence smoking cessation were significantly greater within group NB as opposed to group N as well as group B (P value <0.05) and exhibited insignificant variation among group N as well as group B at 1, 2 and 3 months. Utilizing nicotine inhaler in conjunction with bupropion treatment yielded a rise in smoking cessation rates.

Keywords: Nicotine Inhaler, Bupropion, Smoking, Cessation.

Full length article **Corresponding Author*, e-mail: *drheba632@yahoo.com*

1. Introduction

Smoking is a chronic condition, linked to addiction mostly caused by nicotine. Smokers, on average, exhibit a life expectancy of ten years less as opposed to non-smokers. Additionally, almost half of smokers develop a 20 years' reduction in their overall life quality prior to death due to diseases directly induced by smoking [1-2]. Along with its role in the development of various cancer types, particularly in lungs, smoking is also the primary aetiology of chronic respiratory diseases, involving chronic obstructive pulmonary disease (COPD), and a significant factor in cardiovascular diseases, involving myocardial infraction (MI), stroke, as well as peripheral arterial diseases. Among those having hypertension, even with appropriate blood pressure management, smoking shown to be independently linked to earlier atherosclerosis' indicators [3-4]. Various treatments exist for treating smoking addiction, involving non-pharmacological approaches such as behavioural counselling, as well as pharmacological such as varenicline, bupropion, as along with cytisine [5]. Nicotine oral inhalation is utilized as an aid for smoking cessation. It is advisable to combine nicotine oral inhalation along with a smoking cessation program. Nicotine inhalation belongs to a category of drugs known as smoking cessation aids. Its mechanism of action involves nicotine administration for alleviating withdrawal symptoms linked to smoking cessation as well as diminishing cigarettes' craving [6].

Bupropion is an atypical antidepressant. The precise mechanism by which bupropion exerts its antidepressant effect remains not completely comprehended. However, it is known that bupropion hinders the reuptake of dopamine, noradrenaline, as well as serotonin in z cerebral nervous system (CNS). Additionally, it acts as a non-competitive antagonist of nicotine receptors & at elevated concentrations, suppresses the noradrenergic neurons' activity in the locus coeruleus [7]. The specific mechanism responsible its antismoking efficacy remains uncertain. Nevertheless, it is probable that it could prevent the dopamine as well as noradrenaline levels' decrease in the CNS during nicotine withdrawal. Bupropion's antismoking efficacy seems to be independent of its depressive properties, since it exhibits equal effectiveness in helping smokers quit, regardless of whether they have depression or not [8]. The United States Public Health Service Clinical Practice Guideline recommends utilizing nicotine inhaler as well as bupropion as the first drugs of choice. The nicotine inhaler's efficacy in promoting smoking cessation among smokers was proven. Combining a nicotine inhaler along with bupropion in treatment yielded greater rates of smoking cessation. [6]. Few research has investigated the combination of nicotine inhalers

with bupropion for smoking cessation. Therefore, this research was aimed at evaluation nicotine inhaler and/or bupropion impact on smoking cessation.

2. Patients and Methods

Our prospective randomized comparative study involved 90 smokers aged from 18 to 65 years old, both sexes, smoking at least ten cigarettes daily for a year. Exclusion criteria involved pregnancy or breast-feeding during study entry, utilizing either pharmacological or behavioural therapies for smoking cessation, utilizing tobacco products except cigarettes within a month prior to our research, those having prior allergies to nicotine, bupropion, or menthol (the nicotine inhaler contains menthol), unstable angina or MI within the last 3 months, a prior or present bulimia or anorexia nervosa, seizure disorders, severe head trauma, or other conditions, making them more prone to develop seizures, as well as actively dependent on any substance other than nicotine during the last twelve months, or, consuming antipsychotics, antidepressants, theophylline, systemic corticosteroids, antiepileptic drugs, or a monoamine oxidase inhibitor (due to possible interactions with bupropion).

2.1. Randomization and blindness

The participants went through an equal categorization into three groups utilizing computer generated random number. Group N: (Nicotine inhaler): participant received sixteen cartridges of nicotine inhaler daily. Group B: (bupropion): participant received bupropion 150 mg daily one before their intended quit date then 150 mg two times each day for two to eight weeks. Group NB: (Nicotine inhaler and bupropion): participant received both nicotine inhaler and bupropion. All subjects went through a comprehensive history taking gathering, medical history for exclusion criteria, clinical assessment, and laboratory investigation.

2.2. Nicotine inhaler

Patients were given no less than four and no more than 20 inhalers/day. The dosage of inhaler utilized is not predetermined; intake was a function of inhalers' number utilized * uses' number per inhaler * puffs' number per use. To emphasize the need of frequent inhalation, we instructed participants to utilize at least 4 inhalers daily, administering each inhaler five times with 100 puffs each usage. This totals to 2000 puffs (4 * 5 * 100). Participants were directed to take shallow puffs along with switching to another inhaler in case they perceived it to be ineffective. An inhaler is deemed inactive following four hundred puffs, one day after being opened, or when participants perceive an efficacy loss. Participants were granted permission to utilize inhalers for a maximum duration of 6 months. A protocol for discontinuing the inhalers' usage was implemented following three months. During that period, subjects were given supplies at 75%, 50%, and 25% of their typical three-month consumption levels. This gradual reduction in supply occurred on a monthly basis during the last three months of the pharmacological therapy. Individuals were responsible for implementing the weaning process. At baseline, we assessed the nicotine dependence severity utilizing the Fagerström test for nicotine dependence (FTND). Possible scores of the FTND fall between 0 and 10, score of zero to three exhibits low dependence, four to six exhibiting moderate dependence, while a score from seven to ten exhibits high dependence (Table 1) [9]. The overall FTND score was the research's primary outcome, while the secondary outcomes involved the smoking cessation attempts frequency as well as prevalence smoking abstinence.

2.3. Sample Size Calculation

The sample size calculation was done by G*Power 3.1.9.2 (Universitat Kiel, Germany). We performed a pilot study (10 cases in each group), and we found that Prevalence smoking abstinence at 1 month was 10% in group B and 40% in group NB. The sample size was based on the following considerations: 95% confidence limit, 90% power of the study, group ratio 1:1:1, and four cases were added to each group to overcome dropout. Therefore, we recruited 30 patients in each group.

2.4. Statistical analysis

The statistical analysis performed using SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test as well as histograms were utilized for assessing the normality of the distribution of data. Quantitative parametric data were presented as mean as well as standard deviation (SD) then went through analysis utilizing ANOVA (F) test. Qualitative variables were presented as frequency as well as percentage (%) and were analyzed utilizing the Chi-square test. A 2 tailed P value < 0.05 was deemed to be statistically significant.

3. Results and discussion

3.1. Results

Regarding our research, around 109 cases were evaluated for eligibility, 12 cases did not match our requirements as well as 7 others did not agree to take part in our research. The remaining 90 participants went through a random categorization into 3 equal groups (30 participants within each). All of them went through a follow-up period as well as statistical analysis. Demographic data and educational level exhibited an insignificant variation among all 3 groups Table 2. Age started smoking, number cigarettes smoked, and number of times tried to stop smoking were insignificantly varied among all groups. Overall Fagerström score exhibited insignificant variations among all groups Table 3. Prevalence smoking abstinence was insignificantly varied between group N as well as group B at 1 month, 2 months and 3 months and were significantly greater within group NB as opposed to group N as well as group B (P value <0.05) Table 4.

3.2. Discussion

The nicotine inhaler operates on the principle of nicotine replacement therapy (NRT), which is designed to ease process of smoking cessation by delivering controlled doses of nicotine without the harmful tar and chemicals found in tobacco smoke. Unlike traditional cigarettes, the inhaler doesn't burn or produce smoke; instead, it contains a replaceable cartridge that houses a porous plug saturated with nicotine [10]. When a user draws on the mouthpiece of the inhaler, air is pulled through cartridge, vaporizing nicotine. The user then inhales this nicotine-laden vapour, providing a sensation similar to smoking. This controlled delivery helps manage withdrawal symptoms and cravings, enabling smokers to steadily decrease their nicotine's dependence [11]. It is worth mentioning that however referred to as an "inhaler," most of nicotine is really delivered to mouth (36%) as well as oesophagus and stomach (36%) [12-13].

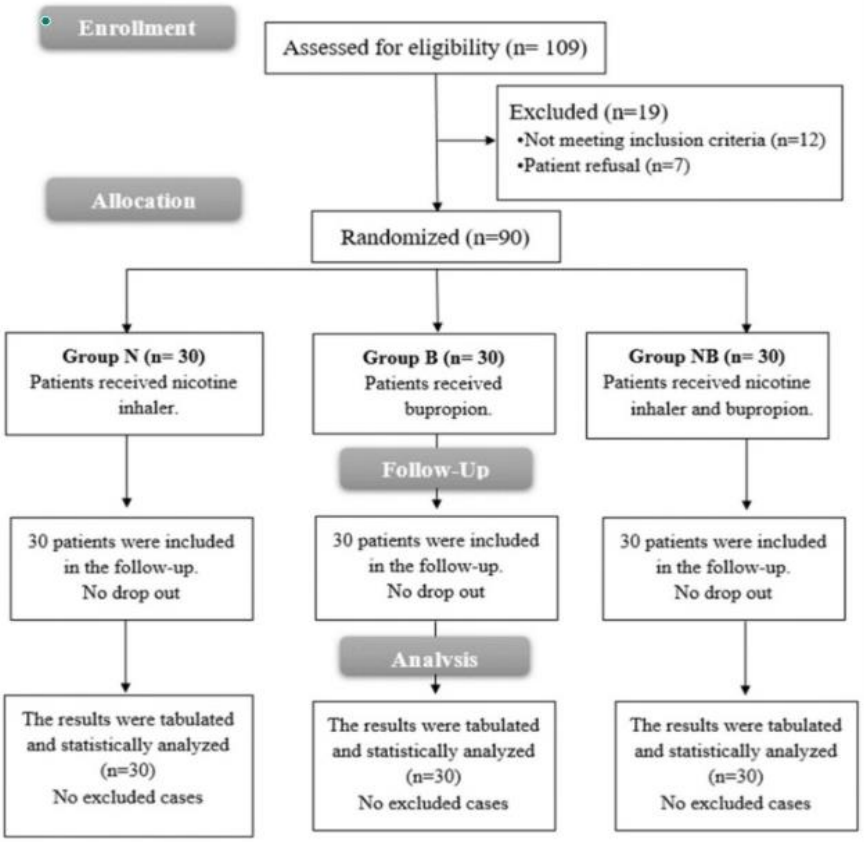

Figure 1: CONSORT flowchart of the enrolled patients.

Table 1: Fagerström test for nicotine dependence (FTND) [9]

1. What is the time interval between waking up and smoking your first cigarette?
   - After five minutes (three points)
   - From six to half an hour (two points)
   - From half an hour to one hour (one point)
   - After one hour (zero points)
2. Do you struggle to abstain from smoking in locations where it is prohibited, such as in churches, libraries, cinemas, trains, as well as restaurants)?
   - Yes (one point)
   - No (zero points)
3. Which cigarette would you find most difficult to quit?
   - First cigarette in the morning (one point)
   - All others (zero points)
4. What is your daily cigarette consumption?
   - Ten cigarettes or less (zero points)
   - From eleven to twenty cigarettes (one point)
   - From twenty-one to thirty cigarettes (two points)
   - More than thirty cigarettes (three points)
5. Do you exhibit a higher frequency of smoking during the first hours after awakening compared to the rest of the day?
   - Yes (one point)
   - No (zero points)
6. Do you engage in smoking even when you are extremely sick, while spending most of your day confined to bed??
   - Yes (one point)
   - No (zero points)

Table 2: Demographic data and educational level of all groups

		Group N (n=30)	Group B (n=30)	Group NB (n=30)	P value
Age (years)		47.2 ± 13.44	41.6 ± 13.37	42.5 ± 13.26	0.223
Sex	**Male**	11 (36.67%)	18 (60%)	19 (63.33%)	0.079
	Female	19 (63.33%)	12 (40%)	11 (36.67%)	
Weight (kg)		77.3 ± 8.71	74.3 ± 9.6	73.5 ± 6.98	0.191
Height (m)		1.67 ± 0.08	1.68 ± 0.08	1.66 ± 0.07	0.468
BMI (kg/m^2)		27.9 ± 4.13	26.4 ± 4.3	26.9 ± 3.1	0.340
Educational level	**Primary education**	5 (16.67%)	7 (23.33%)	11 (36.67%)	0.372
	Diploma graduate	9 (30%)	11 (36.67%)	8 (26.67%)	
	Secondary education	10 (33.33%)	4 (13.33%)	6 (20%)	
	Graduated college	6 (20%)	8 (26.67%)	5 (16.67%)	

Data are displayed as mean ± SD or frequency (%), BMI: Body mass index.

Table 3: Age started smoking, cigarettes' number smoked daily, times tried to cessate, and Overall fagerström score smoking of all groups

	Group N (n=30)	Group B (n=30)	Group NB (n=30)	P value
Age started smoking (years)	18.8 ± 5.47	19.6 ± 4.45	19.8 ± 4.05	0.684
Number of cigarettes smoked per day	25.1 ± 8.54	28.8 ± 4.15	28.7 ± 8.24	0.087
Number of times tried to stop smoking	3.4 ± 1.28	3.5 ± 1.04	2.9 ± 0.99	0.103
Overall Fagerström score	5.3 ± 2.94	5.2 ± 2.92	5.7 ± 2.9	0.772

Data are displayed as mean ± SD.

Table 4: Prevalence smoking abstinence of all groups

	Group N (n=30)	Group B (n=30)	Group NB (n=30)	P value	Post hoc
At 1 month	3 (10%)	5 (16.67%)	13 (43.33%)	**0.005***	P1=0.448 **P2=0.004*** **P3=0.024***
At 2 months	2 (6.67%)	3 (10%)	11 (36.67%)	**0.004***	P1=0.640 **P2=0.005*** **P3=0.015***
At 3 months	1 (3.33%)	2 (6.67%)	9 (30%)	**0.004***	P1=0.554 **P2=0.006*** **P3=0.020***

Data are displayed as number or frequency (%). *Significant as p value ≤0.05. P1: P value among group N as well as group B, P2: P value among group N as well as group NB, P3: P value among group B as well as group NB.

Only a small fraction of nicotine, around four per cent, reaches the lungs. Due to the fact that absorption occurs mostly via oral mucosa, rate of absorption remains comparable to that of nicotine gum. Inhaler cartridge contains 10 mg of nicotine, with a maximum delivery of 4mg and absorption of 2mg by regular "puffing" [14]. One of the key advantages of the nicotine inhaler is its ability to mimic the behavioural aspects of smoking. Many individuals find comfort in the hand-to-mouth action associated with smoking, as well as the inhaler offers to maintain this ritual without the harmful effects of tobacco. The inhaler provides a regulated and predictable nicotine supply [10]. This controlled approach helps users avoid the peaks as well as valleys of nicotine levels experienced with smoking, reducing likelihood of intense cravings. By eliminating the combustion process, the inhaler minimizes exposure to the harmful chemicals and carcinogens present in tobacco smoke. This makes it a safer alternative for those seeking to quit smoking [15]. Some users may experience mild irritation in the throat or mouth when using the inhaler. This side effect is generally temporary and tends to improve with continued use [16]. While inhaler addresses behavioural aspects of smoking, some individuals may find it less satisfying than traditional cigarettes. It's essential for users to be patient and give themselves time to adapt to new method [15].

Bupropion's efficacy in smoking cessation lies in its impact on neurotransmitters, particularly dopamine and norepinephrine, within the brain. Unlike NRTs that provide a controlled dose of nicotine, bupropion is non-nicotine based. Its mechanism of action involves inhibiting the reuptake of dopamine and norepinephrine, thereby elevating their levels in brain. This action is thought to mitigate the withdrawal symptoms and cravings associated with nicotine dependence, contributing to a higher likelihood of successful smoking cessation [17]. Bupropion offers a non-nicotine approach to smoking cessation. This is particularly beneficial for individuals who prefer to break free from nicotine dependence without using replacement substances. By affecting neurotransmitters associated with pleasure and reward, bupropion not only helps manage withdrawal symptoms but also addresses psychological aspects of smoking addiction. This dual action makes it a comprehensive tool in treatment of tobacco dependence [18]. Extended-release formulations of bupropion allow for once-

daily dosing, improving adherence and convenience for individuals undergoing smoking cessation [19]. According to our results, prevalence smoking abstinence exhibited insignificant difference b/w group N as well as group B at 1 month, 2 months and 3 months and were significantly greater within group NB as opposed to group N as well as group B.

Combining a nicotine inhaler along with bupropion emerges as a powerful instrument in the arsenal against tobacco dependence. By integrating controlled nicotine replacement with neurochemical modulation, this approach offers a multifaceted strategy, increasing the chances of successful smoking cessation. As always, individualized care and professional guidance play pivotal roles in optimizing the benefits of this combination, emphasizing the importance of a holistic approach to breaking the cycle of tobacco addiction [6]. Our findings aligned with Croghan et al. [6] reporting that utilizing both a nicotine inhaler as well as bupropion in combination yielded a higher rate of smoking cessation. Prior research has also shown that the combined therapy of a nicotine patch as well as bupropion resulted in greater prolonged rates of smoking cessation as opposed to utilizing either one of these treatments [20]. Benli et al. [21] showed that the smoking cessation rate in the bupropion group was judged to be 6.2% after one year. Nevertheless, when utilizing the 'point prevalence abstinence' test of the American Public Health Service for assessing the smoking cessation success in the last seven days at one year, the rates of success were found to be 20.5% for varenicline and 18.6% for bupropion. No significant statistical variation was seen between the treatments.

A prior systematic review by Siskind et al. [22], showed that the combination therapy was superior to bupropion or other single forms of NRT. In another systematic review which examined 10 studies, findings suggested that varenicline groups achieved higher rates of abstinence compared to both NRT and placebo, bupropion and NRT were of similar effectiveness, and bupropion and varenicline both had higher abstinence rates compared to placebo [21]. According to a prior research by Sheffer et al. [23] completion rate of a 3-month treatment exhibited 40%. Additionally, successful therapy usage linked to communication maintenance. Proactive calls have yielded a rise in success rate [24]. A recent RCT addressed, overall success rate of NRT, bupropion, a combination of NRT and bupropion, as well as a placebo exhibited 14% at 3 months while 8% at 6 months. There was no statistically significant variation documented among the intervention groups (NRT, bupropion, or their combination) as well as the placebo group at 3 and 6 months in terms of success rate. The success rates exhibited 8%, 12%, 8%, and 28% at 3 months, and 8%, 12%, 0%, and 12% at 6 months, respectively [25]. Limitations involve a modest sample size, a single-centered study, a limited follow-up timeframe, as well as not estimating negative events linked to techniques utilized.

4. Conclusions

The nicotine inhaler stands as a valuable tool in the arsenal against tobacco dependence. Combining nicotine inhaler along with bupropion therapy yielded a better result in smoking cessation rates.

Acknowledgement

Nil

References

[1] P. Jha. (2020). The hazards of smoking and the benefits of cessation: a critical summation of the epidemiological evidence in high-income countries. elife. 9: e49979.

[2] Lancet. (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 392: 923-94.

[3] A.H. Mokdad, K. Ballestros, M. Echko, S. Glenn, H.E. Olsen, E. Mullany, A. Lee, A.R. Khan, A. Ahmadi, A.J. Ferrari. (2018). The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. Jama. 319(14): 1444-1472.

[4] C. Wang, J. Xu, L. Yang, Y. Xu, X. Zhang, C. Bai, J. Kang, P. Ran, H. Shen, F. Wen. (2018). Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. The Lancet. 391(10131): 1706-1717.

[5] R. Jiloha. (2014). Pharmacotherapy of smoking cessation. Indian journal of psychiatry. 56(1): 87-95.

[6] I.T. Croghan, R.D. Hurt, S.R. Dakhil, G.A. Croghan, J.A. Sloan, P.J. Novotny, K.M. Rowland, A. Bernath, M.L. Loots, N.A. Le-Lindqwister. (2007). In Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention, Mayo Clinic Proceedings. Elsevier. 186-195.

[7] E. Roddy. (2004). Bupropion and other non-nicotine pharmacotherapies. Bmj. 328(7438): 509-511.

[8] A.M. Rojewski, A.M. Palmer, B.A. Toll. (2021). Treatment of Tobacco Dependence in the Inpatient Setting. In Tobacco Dependence: A Comprehensive Guide to Prevention and Treatment. Springer. 149-162.

[9] T.F. Heatherton, L.T. Kozlowski, R.C. Frecker, K.O. FAGERSTROM. (1991). The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction. 86(9): 1119-1127.

[10] U. Wadgave, L. Nagesh. (2016). Nicotine replacement therapy: an overview. International journal of health sciences. 10(3): 425-435.

[11] J.R. Hughes. (2003). Motivating and helping smokers to stop smoking. Journal of general internal medicine. 18: 1053-1057.

[12] L. Molander, E. Lunell. (2001). Pharmacokinetic investigation of a nicotine sublingual tablet. European journal of clinical pharmacology. 56: 813-819.

[13] J.H. Choi, C.M. Dresler, M.R. Norton, K.R. Strahs. (2003). Pharmacokinetics of a nicotine polacrilex lozenge. Nicotine & Tobacco Research. 5(5): 635-644.

[14] T.C.P.G.T. Tobacco. (2008). A clinical practice guideline for treating tobacco use and dependence:

2008 update: a US public health service report. American journal of preventive medicine. 35(2): 158-176.

[15] H. Tattan-Birch, J. Hartmann-Boyce, L. Kock, E. Simonavicius, L. Brose, S. Jackson, L. Shahab, J. Brown. (2021). Heated tobacco products for smoking cessation and reducing smoking prevalence. Cochrane Database of Systematic Reviews. 1: Cd013790.

[16] Q. Zhang, C. Wen. (2021). The risk profile of electronic nicotine delivery systems, compared to traditional cigarettes, on oral disease: a review. Frontiers in Public Health. 11: 1146949.

[17] A. Clark, B. Tate, B. Urban, R. Schroeder, S. Gennuso, S. Ahmadzadeh, D. McGregor, B. Girma, S. Shekoohi, A.D. Kaye. (2021). Bupropion mediated effects on depression, attention deficit hyperactivity disorder, and smoking cessation. Health psychology research. 11: 81043.

[18] M.E. Mooney, J.M. Schmitz, S. Allen, J. Grabowski, P. Pentel, A. Oliver, D.K. Hatsukami. (2016). Bupropion and naltrexone for smoking cessation: A double-blind randomized placebo-controlled clinical trial. Clinical Pharmacology & Therapeutics. 100(4): 344-352.

[19] S. Howes, J. Hartmann-Boyce, J. Livingstone-Banks, B. Hong, N. Lindson. (2021). Antidepressants for smoking cessation. Cochrane Database of Systematic Reviews. 5: Cd000031.

[20] C.C.L. (2019). Kilmer. Collagen Type I and II Blend Hydrogels for Articular Cartilage Tissue Engineering. Purdue University.

[21] A.R. Benli, S. Erturhan, M.A. Oruc, P. Kalpakci, D. Sunay, Y. Demirel. (2017). A comparison of the efficacy of varenicline and bupropion and an evaluation of the effect of the medications in the context of the smoking cessation programme. Tobacco Induced Diseases. 15: 10.

[22] D.J. Siskind, B.T. Wu, T.T. Wong, J. Firth, S. Kisely. (2020). Pharmacological interventions for smoking cessation among people with schizophrenia spectrum disorders: a systematic review, meta-analysis, and network meta-analysis. The Lancet Psychiatry. 7(9): 762-774.

[23] C.E. Sheffer, M. Stitzer, R. Landes, S.L. Brackman, T. Munn, P. Moore. (2012). Socioeconomic disparities in community-based treatment of tobacco dependence. American journal of public health. 102(3): e8-e16.

[24] W. Pan. (2006). Proactive telephone counseling as an adjunct to minimal intervention for smoking cessation: a meta-analysis. Health education research. 21(3): 416-427.

[25] D.A. Abdelghany, N.M. Shalabi, A.M. Abd-El-Maksoud, W.A. El-Bahaey, M.S. El-Dahan, N.S. Farrag, T.A. Elhadidy. (2021). Efficacy of nicotine-replacement therapy, bupropion, and a combination of both for treating nicotine addiction: a randomized clinical trial. The Egyptian Journal of Chest Diseases and Tuberculosis. 71(1): 51-58.