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THE EFFECT OF LOW DOSE NICOTINE ON WORKING MEMORY AND POSITIVE EMOTION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

Zeinab Samnia[1], Zhila Yousefi[2], Naveena JH[3], Imran Khan[4], Abbas Rouzbahani[5], Esmail Khodadadi[6]*

[1]Master degree in Clinical Psychology, Department of Psychology, Faculty of Allameh Jafari, Islamic Azad University of Tabriz, Tabriz, Iran. E-mail: zeynab.samnia64@gmail.com.
Tel: +989371746504. ORCID: https://orcid.org/0000-0003-1859-9173
[2]Master degree in nursing, Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran. E-mail: zhilayousefi21@yahoo.com. Tel: +989147758046.
ORCID: https://orcid.org/0000-0001-5067-1687
[3]PhD in Nursing, Department of Community Health Nursing, Vice Principal, Govt College of Nursing GSVM Medical College campus Kanpur.
E-mail: jhnaveen@gmail.com. Tel:+917534064460. ORCID: https://orcid.org/0000-0003-2564-0787
[4]PhD in Nursing, Department of Medical Surgical Nursing, Narayan Nursing College, Gopal Narayan Singh University, Jamuhar, Rohtas, Bihar.
E-mail: imrankhanlalkhanawar@gmail.com. Tel:+918277363922.
ORCID: https://orcid.org/0000-0002-1428-58075
[5]Master degree in nursing, Department of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran.
E-mail: abbas.rozbahani@gmail.com. Tel: +989183537426.
ORCID: https://orcid.org/0000-0002-4101-4957
[6]*PhD in Nursing Education, Iranian Social Security Organization, Urmia, Iran.
Email: esmailkhodadadi11@gmail.com. Tel: +989143481951.
ORCID: https://orcid.org/0000-0003-3124-4166

***Corresponding Author:** Esmail Khodadadi
*PhD in Nursing Education, Iranian Social Security Organization, Urmia, Iran.
Email: esmailkhodadadi11@gmail.com, Phone number: +989143481951,
Fax number: +984433659928

Abstract

Background: The persons with Mild Cognitive Impairment are more likely to develop dementia. This condition can lead to permanent memory impairment and dementia if left untreated. So far, several non-pharmacological treatments have been used to prevent the progression of this disorder, but their effectiveness needs to be further investigated. The aim of this study was to determine the effectiveness of low dose nicotine on working memory and positive emotion in patients with mild cognitive impairment.

Methods: This is a quasi-experimental study with a control group. Fifty male patients referred to neurology clinics in Tabriz city were selected by convenience sampling method and randomly assigned to the control and experimental groups. Data collection tools included Wechsler Memory Scale (WISC-IV) and Positive and Negative Affect Schedule (PANAS). Data were analyzed using SPSS software ver. 24.

Results: The findings indicated that the mean scores of working memory and positive emotion in experimental group were not statistically significantly different from the control group before intervention ($P>0.05$). But after intervention the mean scores of working memory and positive emotion in experimental group were statistically significantly higher than the control group ($P<0.05$).

Conclusion: The study findings indicated that low dose nicotine enhances working memory and increases positive emotions in patients with mild cognitive impairment. Therefore, the findings of this study can be used in the treatment and rehabilitation of patients with mild cognitive disorders.

Keywords: Low dose nicotine, Working memory, Positive emotions, Mild cognitive impairment.

Introduction

Mild cognitive impairment (MCI) is defined by a significant decrease in cognitive function that goes beyond the natural changes that are caused by aging. There is currently no clear cure for MCI, and no and many experimental treatments currently available and in the future will focus on secondary prevention, i.e. reducing the risk of major cognitive disorders.[1] According to the evidences, due to the loss of large cells in the hippocampal region of the brain caused by aging, 5 to 20% of people Over 65 years old suffer a MCI. It is not a type of dementia, but a person with this disorder is severely prone to dementia. In some people, MCI stabilizes over time, and in others, it improves.[2] Memory is damaged more than anything else in MCI. Such as slowing down information processing, lack of focus and attention, Defects in executive functions, Cognitive problem-solving processes, Planning and other management brain activities including metacognition and self-regulation, visual cognition skills deficits including object recognition deficits and sense of direction finding in place and space, fluency of speech, defects in verbal intelligence, defects in general intelligence plus defects in mood and personality.[3]

There are several types of memory including: Short-term memory, active memory or working memory, and long-term memory. Short-term memory refers to the events that have occurred in the last few seconds that involve visual and audio memory. First, Information is perceived by the sensory memory through the senses. Then it is transferred to short-term memory during 1 to 4 seconds. This information is stored in short-term memory for about 20 to 30 seconds which does not have a large capacity and can only hold about 7 items in a short time. Then information is transferred to working memory for processing. There, processing begins and appropriate responses are generated and in working or active memory, information is temporarily and limitedly stored, processed and used, and then stored in long memory. An unlimited amount of information and long-term memories are stored there. When someone forgets something it is usually have two reasons: that information is not encrypted properly or there is a problem in memory retrieval.[4,5]

Regarding aging and its effect on memory, scientists have offered many theories on how memory decreases in elderly. But most of these theories agree on the principle that acetylcholine-transporting cells are destroyed with age and the reason for this is that the neurotransmitter acetylcholine is essential for memory production.[1] There are many treatments for this disorder some of which are briefly mentioned: Cognitive enhancers such as cholinesterase inhibitors and Memantine. Polyphenolic compounds to enhance antioxidant and anti-inflammatory activities that can reduce degradation caused by nervous progress. Non-pharmacological treatments such as exercise, stimuli cognitive, computer cognitive exercises, serotonin reuptake inhibitors and psychological interventions can reduce the progression of nerve damage.[6] However, among these treatments, many side effects and minor effects have been reported. Evidence shows that Nicotine molecule binds to acetylcholine receptors. These receptors can have tremendous capacity to modulate other receptors by calming and enhancing their function. Based on the evidence, nicotine receptors in the brain work by regulating other acetylcholine receptor systems.[7,8] In addition Nicotine primary transmitter, which is dopamine, plays an important role in regulating attention to operant conditioning and drug addiction and movement and this answers the question of why nicotine can cause movement disorders such as Parkinson's due to its effects on dopamine responds to slow prevention.[9]

Research results show that nicotine may protect the patient against Alzheimer's in the early stages of the disease [10]. The results of Robinson's study showed that nicotine stimulation in the short term can affect memory, improve attention and speed. He also found that nicotine was safe since in his research and he did not see any side effects and symptoms after nicotine use in non-smokers.[11]

Patients with memory impairment often have low mood due to inability to remember important activities. Feeling depressed and afraid of worsening cognitive status in these patients makes them have less life expectancy. Evidence shows that nicotine can improve memory impairment and sad mood of these patients in the early stages of the disease. As a result, elevated mood and improved memory in these patients increase the life expectancy and a sense of empowerment.[12] Given that in this regard there is

no general agreement on the positive effect of nicotine on boosting the memory and mood in patients with MCI, so more research is needed. On the other hand, due to the lack of studies in this field, especially in Iran, more research about nicotine and its therapeutic mechanism seems necessary. So this study was conducted to investigate the effect of low dose nicotine on increasing working memory and positive emotion of patients with mild cognitive impairment.

Materials & Methods

2.1 Study design

The present study is a quasi-experimental (pre-test & post-test) study with a control group.

2.2 Study Participants

The statistical population includes all male patients aged 20 to 60 years with MCI of Tabriz city in Iran. Research samples include 50 eligible male patients aged 20 to 60 years to be referred to neurology clinics for treatment in May 2021. The sample size was determined based on previous similar studies.[13] Samples were selected by convenience sampling method and were randomly assigned into two groups by using computer random-number generators software: control and experimental (25 patients in each group). Then two groups were made in terms of demographic characteristics of homogeneous samples. Inclusion criteria were: definitive diagnosis of MCI, no heart or brain disease and, no use of physical and psychiatric drugs except drugs for cognitive disorders, no hypertension and non-smoking. Exclusion criteria were: unwillingness to participate in the research or study withdrawal, incidence of side effects after nicotine use. The research was carried out after coordinating with the director of the centers and obtaining an ethical approval code from Islamic Azad University of Tabriz.

2.3 Intervention

Data collection tools included demographic characteristics of samples, Wechsler width test and PANAS (Positive and Negative Affect Schedule) questionnaire. After completing the questionnaires in the pre-test stage, the patients in the experimental group received chewing gum containing 2 mg of nicotine and patients in the control group also received non-nicotine gum. It was recommended to these patients to chew gum very gently because it would irritate the mouth and while chewing vital signs of people who felt uncomfortable was being controlled. Fortunately, none of the people developed abnormal symptoms. After 2 hours of intervention time, participants completed the questionnaires again.

2.4 Instruments

Wechsler Memory Digits Broadband Subtest: broadband test of numbers is an adult revised version of Wechsler test that has been designed in two parts of range of direct and inverse.[14] This test includes: Multiple sequences of numbers that are presented to the subject by audio and the subject must order the numbers in straight and reverse order. In the direct part, the series of numbers starts from 4 digits and after each

presentation a digit is added to the chains of numbers to make a maximum of 8 digits. Scores in this section are determined according to the last digit that the subject has been able to repeat. Direct part scores and inverse part scores are each calculated separately. The range of scores for repeat forward digits is 1 to 8, and range of scores for repeat backward digits is 1 to 7. The higher score indicated the stronger memory. In Yadollahi's research (2016) Cronbach's alpha coefficient for verbal and practical subscales was declared 0.82 and 0.71 respectively.[15] The reliability of this tool in Cornoldi research (2013) using Cronbach's alpha method was reported 0.75 to 0.90.[16] PANAS Scale is a 20-item tool used to measure two mood dimensions, negative and positive emotion which is designed by Watson *et* al. in 1988.[17] Each subscale has 10 items. Items are rated on a Likert scale of 5 points (1= very low to very high = 5). The overall range of scores for each subscale is 10 to 50 and a higher score indicates positive emotion. Reliability of this questionnaire in the study of Mani *et* al. (2019) using Cronbach's alpha coefficient was 0.85.[18] and in the Díaz-García study (2020) Cronbach's alpha coefficient were calculated from 0.87 to 0.91.[19]

2.4 Statistical analysis

Data was analyzed by SPSS statistical software ver. 22 for descriptive statistics (number, percentage, mean, and standard deviation) and inferential statistics (Chi-square, independent t-test and paired t-test). The Kolmogorov-Smirnov test results indicated the normality of the data distribution before using the parametric test to analyze the data with a statistical significance level set for less than 0.05.

2.5 Ethical considerations

This study was approved by the Ethics Committee of Islamic Azad University of Tabriz. (Ethical approval No: IR.IAU.TABRIZ.REC.1397.032). Informed consent was obtained from all participants with emphasis on data security, confidentiality, privacy and freedom to join or withdraw from the study at any time.

Results

The average age of participants was 52.04±3.28. Most of the participants were married and had a diploma. Results of study showed that no significant differences between two groups (Control and Experimental) based on their demographic characteristics. Table (1)

Table 1. Demographic characteristics of participants

Variables		Group: Control n (%)	Group: Experimental n (%)	p-value
Marital status	Single	6 (24.0)	8 (32.0)	$0.745=X^2$
	Married	19 (76.0)	17 (68.0)	$p= 0.38$
Academic level	Elementary	8 (32.0)	7 (28.0)	$0.588=X^2$
	High school	14 (56.0)	16 (64.0)	$p= 0.43$
	Bachelor	3 (12.0)	2 (8.0)	
Economic status	Weak	6 (24.0)	5 (20.0)	$0.121=X^2$
	Moderate	15 (60.0)	17 (68.0)	$p= 0.75$
	Good	4 (16.0)	3 (12.0)	
Residence location	Urban	21 (84.0)	19 (76.0)	$1.68=X^2$
	Rural	4 (16.0)	6 (24.0)	$p= 0.19$
Age (year)		Mean ± SD	Mean ± SD	$t = 1.02$
		51.46±3.12	53.62±3.45	$p= 0.28$

x^2= Chi-square test; t= Independent samples t-test; SD= Standard deviation

The results showed that the mean score of direct working memory before intervention in control and experimental group were 2.9±0.6 and 3.0±0.6 respectively. Also, the results showed that there was not a significant difference between them (p>0.05). But the mean score of direct working memory after intervention in the control and experimental group were 2.8±0.5 and 4.1±0.5 respectively. The results also showed that there was a statistically significant difference between control and experimental group (p<0.05) Table No (2).

Table 2. Comparison of direct working memory scores in experimental and control groups before and after intervention

Variable	Group	Pre test (*Mean ± SD*)	Post test (*Mean ± SD*)	Paired t-test
Direct working memory	Experimental	3.0±0.6	4.1±0.5	t = 4.86 p= 0.01*
	Control	2.9±0.6	2.8±0.5	t = 0.43 p= 0.67
	Independent t-test	t = 0.29 p= 0.77	t = 5.42 p= 0.01*	

* indicates statistical significant (p<0.05)

Also, the results also showed that the mean score of inverse working memory before intervention in the control and experimental groups were 2.1±0.3 and 2.2±0.4 respectively, and there was not a statistically significant difference between them (p>0.05). But after intervention, the mean scores of inverse working memory in the control and experimental groups were 2.2±0.4 and 3.2±0.4 respectively. The results of independent t-test showed that there was a statistically significant difference between the control and experimental groups (p<0.05). Table No (3)

Table 3. Comparison of inverse working memory scores in experimental and control groups before and after intervention

Variable	Group	Pre test (*Mean* ± *SD*)	Post test (*Mean* ± *SD*)	Paired t-test
Inverse working memory	Experimental	2.2±0.4	3.2±0.5	t = 3.42 p= 0.02*
	Control	2.1±0.3	2.2±0.4	t = 1.46 p= 0.17
	Independent t-test	t = 0.47 p= 0.64	t = 3.46 p= 0.02*	

* indicates statistical significant (p<0.05)

Finally, the results of our study showed that the mean score of positive emotion before intervention in the control and experimental groups was 52.01±1.2 and 52.42±1.5 respectively, and no statistically significant difference was observed between them (p>0.05). But after intervention, the mean scores of positive emotion in the control and experimental groups were respectively 52.56±1.4 and 58.01±2.3. The results of independent t-test showed that there was a statistically significant difference between the control and experimental groups (p<0.05). Table No (4)

Table 4. Comparison of positive emotion scores in experimental and control groups before and after intervention

Variable	Group	Pre test (*Mean* ± *SD*)	Post test (*Mean* ± *SD*)	Independent t-test
Positive emotion	Experimental	52.42±1.5	58.01±2.3	t = 7.22 p= 0.01*
	Control	52.01±1.2	52.56±1.4	t = 1.02 p= 0.32
	Paired t-test	t = 0.91 p= 0.37	t = 6.85 p= 0.01*	

* indicates statistical significant (p<0.05)

Discussion

The aim of this study was to determine the effectiveness of nicotine in increasing working memory and positive emotion in patients with MCI. The results of present study showed that there was a statistically significant difference between the scores of working memory and positive emotion between the experimental and control groups after intervention. This means that nicotine increases working memory and positive emotion in patients with MCI. This finding is consistent by the results of researches done by Sutherland *et* al., Kutlu *et* al., Jensen *et* al., Bombardi *et* al., Grus *et* al., and Grundey *et* al.[20-25] In this regard, the result of Hahn *et* al. have shown that nicotine has cognitive enhancers including improved fine motor functions, attention, working memory, and episodic memory.[26] Also, the results of Myers *et* al. showed that people who used nicotine nasal spray, had better cognitive performance and more computational power comparing to the control group.[27] Newhouse *et* al. concluded in their study that chronic nicotine therapy for cognitive function and memory in the elderly are beneficial, and nicotine therapy improves attention in the elderly who suffer

mild cognitive function.[28] Finally, Nop *et* al. examined the benefits of nicotine use and its important role in maintaining cognitive cues as a way to improve nerve damage in old age.[29] that is consistent with our results.
In order to explain the findings, it can be said that acetylcholine which is hydrolyzed by the enzyme cholinesterase enters the synaptic cleft in a few milliseconds after its release. Nicotine then crosses the synapse in cleft and binds to nicotine Acetylcholine receptors and activates it, which is longer than the nicotine receptor by the agonist. This active prolonged exposure of the receptor to nicotine intake causes receptors to become insensitive and consequently its temporary ability is reduced by Nicotine agonist activity.[30] Most nicotinic acetylcholine receptors in the brain direct several neurotransmitters including Serotonin, Glutamate, Gamma-Aminobutyric acid (GABA) and Norepinephrine.[31,32]

Primary targets of nicotine effect on nicotinic Acetylcholine receptors (nAChRs) are including Ligand ion channels consisting of different pentameric compounds of 9 subunits a (a2a10) and 3 subunits β (β2β4) which are around central different pores and are permeable to sodium, potassium, and calcium ions. Most nAChR nerves act fast in CNS stimulants and balance the release of other neurotransmitters including Acetylcholine, Dopamine, Serotonin, Glutamate, GABA and Norepinephrine.[33,34] Although the effects of nicotine on desensitization and positive regulation of nAChRs is clear, the role of these processes in the cognitive effects of nicotine is complex and incomplete.[35] Evidence suggests that both areas of the anterior cortex of the brain and brain hippocampus are involved in the cognitive effects of nicotine, and cognitive enhancement may be due to improved signal noise or facilitation of synaptic ductility in specific neural circuits.[21] At the clinical level, evidence shows that α7 nAChRs play a role in cognitive deficits in many neuropsychiatric disorders including Alzheimer's disease, Parkinson's disease, autism spectrum disorders and schizophrenia.[36]

Heishman et al. in their study to investigate the direct cognitive effects of nicotine, found that nicotine had significant positive effects on fine motor skills, short-term episodic memory, and working memory performance.[37] that is consistent with the our results. In addition, the results of the study by Posner *et* al. showed that nicotine consumption has a positive effect on maintaining alertness and paying attention to sensory events. However, the effect of nicotine on cognitive function is not dose-dependent throughout, indicating the heterogeneous pharmacodynamics nature of nicotine.[38]

In addition to these findings in long-term smokers, studies also show differences in the effect of nicotine on cognitive function among smokers and non-smokers. While nicotine consumption improves working memory performance in non-smoker individuals, but no improvement was observed in smokers' working memory function.[25] On the other hand, the results of Valentine *et* al. showed that the cognitive enhancing effects of nicotine may contribute to mood enhancing or mood stabilizing effects.[12] Altogether, the results of studies show that nicotine has different effects on

human cognition based on smoking history and status. Nicotine withdrawal depends on the time of the test, and that the cognitive increase due to smoking may be altered by the change in bias Smokers' attention and have fewer effects on mood.[39]
In Stein *et* al. study, the nicotine used intravenously in non-deprived smokers. Nicotine Increased signals that depends on the level of oxygenation in the blood in a number of subcortical and cortical regions related to reward and cognitive function.[40] In another study that used nicotine gum, a marked increase in the signal in the frontal and parietal areas of the brain was reported.[41] The results of Falcon *et* al. showed that people with psychological disorders such as depression and schizophrenia often try smoking to improve concentration and short-term memory [42], which is consistent with the results of the present study.
Also, the results of studies on the effect of nicotine on cognitive function show that nicotine definitely improves motor skills, attention and accuracy and short-term memory response time and long-term memory.[1,12,43] For example the use of nicotine patch and nicotine administered intravenously have had positive results in Alzheimer's patients, including improved memory, increased attention, accuracy and memory time.[1] The results of McClernon *et* al. showed that low-dose nicotine temporarily reduces depression when used in non-smokers.[44] Also the results of Trojak *et* al. showed that nicotine gum therapy reduced negative mood associated with withdrawal more compared with placebo [45] that is consistent with the results of our study. In this regard, the results of other studies also show that the negative mood caused by withdrawal symptoms in smokers are eliminated by using nicotine substitutes in the form of drugs or chewing gum or nasal spray, as a result the positive mood increases [27,31,46] which is consistent with the our results.
Lack of control of intervening variables such as environmental conditions, emotional state and personal issues of the subjects, small numbers of samples were some of the limitations of this study that could affect the generalization of the findings to other populations.

Conclusion

The results of the present study showed that low-dose nicotine consumption can improve working memory and positive emotion in people with MCI. Therefore, according to the findings of this study, nicotine can be used to treat cognitive deficits in patients with MCI, Alzheimer's and other cognitive deficits. We hope that with recognizing the therapeutic Nicotine benefits through further research and testing, nicotine can be given to people with cognitive impairments in the form of drugs and that Nicotine can be used as a new treatment in these patients.

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Conflict of interests
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Conflict of interest/Competing interests
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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors' contributions
All co-authors have contributed to the manuscript according to requirement of full authorship. All authors were involved in design, report writing and approval of final manuscript. EKH and ZS performed main idea, conceptualization, methodology, and software. ZhY and AR performed acquisition of data, analysis and interpretation of data. Njh and IKh performed discussion and language revision.

Ethics approval
This study was approved by the Ethics Committee of Islamic Azad University of Tabriz. (Ethical approval No: IR.IAU.TABRIZ.REC.1397.032).

Consent to participate
Informed consent assured patients of anonymity, freedom to withdraw from the study at any time and data security.

Consent for publication
Not applicable.

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Contribution of the Paper:
- The results of the present study showed that low-dose nicotine consumption can improve direct and inverse working memory in people with MCI.
- The results of the present study showed that low-dose nicotine consumption can improve positive emotion in people with MCI.
- There are several studies that support our results. No study was found that was inconsistent with the results of our study.

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