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EFFECTIVENESS OF GUANFACINE IN SMOKING CESSATION - A SYSTEMATIC REVIEW

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Keywords:

Guanfacine, Smoking, Smoking cessation, Systemic review, Case and control trials, Interventions and outcomes

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ABSTRACT: Background: Guanfacine is a drug used to treat ADHD (attention deficit hyperactivity disorder) and treatment for hypertension from 1986, approved by the FDA. Recently it had been deduced that Guanfacine could also be employed in smoking cessation as a pharmaceutical aid. This could be attributed to the physiological effect that the drug has on the human body, such as decreased heart rate and blood pressure. An increase in heart rate and blood pressure leads smokers to light up a cigarette to ease their stress. Therefore, Guanfacine could be used potentially for nicotine cessation. Guanfacine could be used in combination with other conventional drugs already existing for this very purpose. It has to be mentioned that before employing this drug in the use of smoking cessation, a lot more studies have to be conducted with a much greater sample size to assess if there are any other adverse effects or any other limitations which could vary among different individuals and also assess the optimal amounts of dosage that would be recommendable. Hence, Guanfacine could be a potential drug to help overcome the addiction to nicotine. Aim: To assess the effectiveness of Guanfacine in tobacco cessation. Study Design: A systematic review based on the various clinical trials and the co-related studies on this concept. Thirty-three electronic and hand records were obtained and screened for procuring information for systematic reviews. **Results:** Five studies were selected with information about the clinical trials and randomized controlled trials. **Conclusion:** The studies analyzed show that there is limited evidence to support the effectiveness of Guanfacine in the use of smoking cessation. There is scope for future studies on the effectiveness of the drug.

INTRODUCTION: An epidemic attributed solely to both smoke and smokeless forms of tobacco use has been prevailing among the population of India. Health issues caused by tobacco use have been similar worldwide without any exception [1]. Even if the graph of tobacco uses among the population declines, the consequential graph would still prevail (would still be active).

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There are several smoked tobacco products, namely cigarettes, cigars, bidis, kreteks, pipe, or hookah, among which cigarettes are the most prevalent, and it is mainly gender-specific to males with exceptions in some situations. Similarly, in smokeless tobacco products, including gutka, snuff, khaini, betel quid, zarda, most are used by the Indian population irrespective of gender [2].

Nicotine, an alkaloid extracted from the leaves of Nicotiana tabacum and Nicotiana rustica, is the most potent and highly addictive pharmacological agent accountable for several psychological effects precipitated in tobacco users. The psychological effects of nicotine comprise depressed cognitive function, reduced appetite and heightened mood.

It is mainly because of its promising psychological effects that nicotine is popular among the population. The main driving force that leads adults to use tobacco from a younger age is stress and cognitive dysfunction. There are no therapeutic options easily available to adapt to relieve that particular stress due to which they turn to tobacco, which is easily obtainable, thus leading to an addiction. An added cause for tobacco use could be peer pressure among young adults and even teens in some cases [3, 4].

The most conventional method of tobacco cessation counseling in Public Health studies includes 5A's, namely Ask, Advice, Assess, Assist and Arrange, followed by 5R's, namely Relevance, Risk, Rewards, Roadblocks, Repetition. These methods also help us assess the patient's willingness to control their addiction. And also helps the health care worker chalk out a personalized plan to help the patient break free from their addiction. In addition, there are various methods in which the health care workers can extend their help to the patients who are willing to cope with their addiction [5]. For example, a global adult tobacco survey (GATS) was launched in February 2007, which branched off from the existing global tobacco surveillance system (GTSS) as a medium to record data on tobacco use by adults and tobacco cessation measures. The sequel of the GATS survey enabled the 30 low and middle-income countries to record various tobacco cessation intervention measures and to help collate the outcomes among the countries participating [6].

The GATS survey was conducted in India in two phases, piloted for persons aged 15 or more. The GATS covered all the 30 states as well as two union territories. This household survey weighed up the data procured by two separate data collected throughout GATS -1 and GATS -2 administered in 2009-2010 and 2016-2017, respectively, which Tata Institute of Social Sciences Mumbai orchestrated. As claimed by the Ministry of Health and Family Welfare, Government of India, 74,037 randomly selected persons were approached for an individual interview in August 2016 through February 2017. Pharmaceutical aid to support people in nicotine withdrawal is the most prescribed option by health care workers worldwide for patients to overcome their addiction [7]. An ideal pharmacological option that should be employed in nicotine cessation would be defined as a drug that could ease the user's stress and pave the way for a considerably smooth and serene withdrawal from nicotine. Pharmaceutically, there are two types of smoking cessation aids: nicotine and without nicotine aids. In nicotine-containing options, the FDA-approved method of NRT (Nicotine replacement therapy) where the users are encouraged to gradually decrease their use of nicotine with the help of nicotine skin patches (Nicotex patch by Cipla), Chewing gums (Nicotex chewing gum by Cipla), and Lozenges. The FDA has approved drugs that might help the users and keep them motivated through their withdrawal journey in options without nicotine. There are mainly two FDA-approved drugs used conventionally for tobacco cessation and withdrawal: Varenicline tartrate (Chantix - Trade name) and Buproprion hydrochloride (Zyban - Trade name) [8].

In recent clinical trials, it was deduced that Guanfacine also affected tobacco cessation in the users. The drug Guanfacine, an alpha2A - adrenergic receptor agonist, is known in cases of ADHD (attention deficit hyperactivity disorder). Guanfacine is pharmacologically well known for its effect on decreasing the person's heart rate and bringing a person's blood pressure under control. For the drug to help the user cope with depression and stress, the main mechanism of action of the drug should be on the noradrenergic system. The patient's main concern and the health care worker helping them would be the fear and stress of relapse. Guanfacine, which acts mainly on the noradrenergic system, would be the perfect choice for helping the patient cope with that stress and focus on their day-to-day activities. Guanfacine was found helpful for persons in nicotine withdrawal by decreasing their withdrawal symptoms significantly by decreasing their stress [9].

MATERIALS AND METHODS:

Study Design: A systematic review based on clinical trials was conducted to assess the effectiveness of Guanfacine as a pharmaceutical option to aid in smoking cessation.

Search Strategy: A set of electronic databases was utilized to search for published articles regarding

the effectiveness of Guanfacine as a pharmaceutical option to aid in smoking cessation. The electronic search engines are PubMed, Ovid Medline, Elsevier science direct, Wiley online library, Grey literature, Cochrane Library, Cinahl, Prospero, OSF, Scopus.

Mesh terms were used as keywords to find related topics in the mentioned databases. The mesh terms used was "Guanfacine" AND "smoking/smoking cessation". After the search, 460 articles were found, among which six articles were selected for further discussion.

Eligibility Criteria:

Inclusion Criteria Include:

1) English language articles.
2) Studies based on the effectiveness of Guanfacine in smoking cessation.
3) Studies where clinical trials have been conducted.
4) Full-text articles.
5) Studies conducted from 2014 attributed to the novel idea.

Exclusion Criteria:

- ✓ Other language articles.
- ✓ Abstracts only published articles.
- ✓ Articles that is unrelated to the topic.
- ✓ Studies involving animals.
- ✓ *In-vitro* studies.

Search Engines Used:

- Pubmed
- Cochrane
- Medline
- Lilacs
- Science direct
- Grey literature
- Wiley Online library
- Ovid Medline

RESULTS: Table 1 shows the characteristics of the individuals included in the study. The distribution of participants according to the case and control group is elaborated along with the patients' criteria. The sample size in each study is categorized according to the study groups.

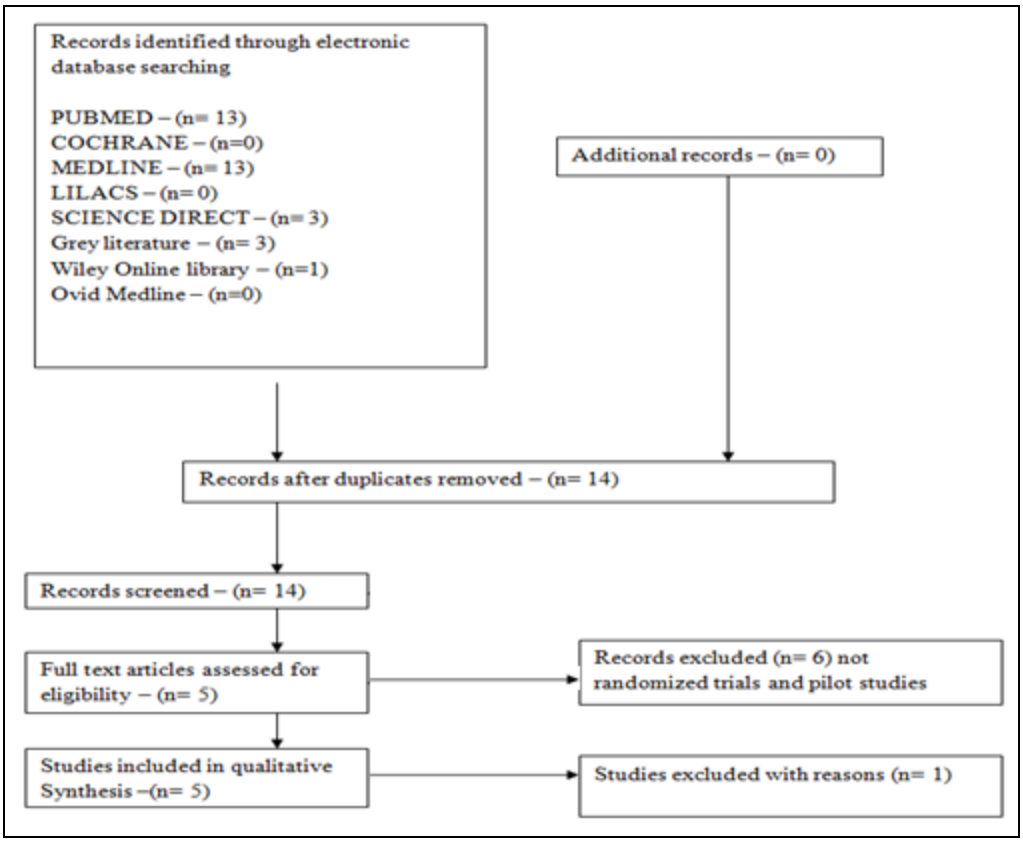

FIG. 1: PRISMA DIAGRAM SHOWING THE FINAL SYNTHESISED ARTICLES INCLUDED IN THE SYSTEMATIC REVIEW

TABLE 1: CHARACTERISTICS OF THE INDIVIDUALS INCLUDED IN THE STUDY

Author name	Year	Sample size	Patient Characteristics	Duration	Number (Case/Control)
Varplatese *et al.* [10]	2019	5	Recruited participants were of age 18-65 and had a smoking frequency of 10 or more cigarettes every day for the past one year	46 days	Participants were subjected to 3 different doses of Guanfacine for different periods of time. First set consisted of 3mg/d of IR Guanfacine, Second set consisted of 3mg/d of ER Guanfacine while the third set consisted for 6mg/d of ER Guanfacine
Sandiego *et al.* [11]	2017	28	Recruited participants were of age 37 ± 9 also they had undergone a medical examination and exhibited no specific medical sickness	3 weeks	Category 1 – 16 participants were not treated by the drug Guanfacine Category 2 – 12 participants were treated using the drug Guanfacine post administration of amphetamine
Mathai *et al.* [12]	2017	7	Recruited participants through advertisements with a prior history of cannabis usage before the age of 18	Two separate time spans of 8 days. Totally 16 days.	Category 1 – were placed under 3mg/day of Guanfacine for the first 8 days and under placebo for the other 8 days Category 2 – were placed under placebo for the first 8 days and under 3 mg/day of Guanfacine for the next 8 days
Varplatese *et al* [13]	2016	26	Recruited participants were of age 18-60 and had a smoking frequency of 10 or more cigarettes per day	3 weeks	Category 1 – 12 participants were placed on a placebo Category 2 – 14 participants were placed on 3mg/day Guanfacine
McKee *et al* [14]	2014	33	Recruited participants selected of age 18-60 and had a smoking frequency of 10 or more cigarettes every day for the past one year	58 days	Category 1 – 17 participants were on Guanfacine Category 2 – 16 partcipants were on a placebo

Table 2 shows the characteristic features of the outcome included in the studies for systematic review. This table clearly shows that guanfacine is an essential drug to treat smoking cessation with minimal adverse effects.

TABLE 2: CHARACTERISTIC FEATURES OF THE OUTCOME INCLUDED IN THE STUDY

Author Name	Year	Effect measure	Results
Varplatese *et al*	2019	Following the study's procedure, the subject's vital signs were assessed during the laboratory sessions as well as blood was drawn and tested for Guanfacine levels in the blood. Also, the subjects were asked to assess themselves using a questionnaire provided	The study's main aim was to determine the pharmacodynamics and pharmacokinetics of Immediate-release and Extended-release Guanfacine in Adult daily smokers. With the limitation of smaller sample size, the results determined that the 3mg/d IR Guanfacine had a considerable efficacy; that being said, the doses 4mg/d and 6mg/d of ER Guanfacine should be studied further before coming to a conclusion.
Mathai *et al*	2017	Following the administration of Guanfacine and placebo to their respective participant pools; Cognitive tests comprising of the revised Hopkins Verbal Learning Test (HVLT), Dual-back test and Continuous Performance test (CPT) were taken by the participants.	The main aim of this study was to determine if Guanfacine attenuates adverse effects of Dronabinol on working memory in adolescent-onset heavy cannabis users. The study results suggest that the combination of Guanfacine with THC controlled the primary adverse effects caused due to THC.
Sandiego et al	*2017*	Following the procedure of the study conducted the ability of resistance exhibited by the subjects towards smoking-induced by positive reinforcement and also calculated the	The study's main aim was to determine if Guanfacine had an effect on the dopaminergic tone in tobacco smokers. The study deduced that Guanfacine did have an effect on the

		number of cigarettes used while the allocated time period for the subject to smoke	dopamine levels on the subject after guanfacine administration for 3 weeks, thus determining that Guanfacine can be potentially used as an aid for tobacco cessation.
Varplatese *et al*	2017	Following the procedure of the study to be conducted, the Variability of Heart rhythm was recorded for the required for observing the frequency of the recorded data for desirable results	The main aim of this study was to determine if Guanfacine alters the effect of stress and smoking on heart rate variability. The study results suggest Guanfacine could be designated as a potential pharmaceutical aid used for tobacco cessation as it significantly alters the heart rate variability in regular smokers.
McKee *et al*	2014	Following the procedure of the study, the subject was observed based on the craving to smoke; the number of cigarettes smoked during the Time period allocated was recorded but not included in the article. Secondarily the mood during nicotine withdrawal was assessed along with the vital signs, cortisol, ATCH levels, Guanfacine levels in the blood drawn were measured at particular time intervals	The study's main aim was an investigation targeting stress reactivity and prefrontal cognitive control with guanfacine for smoking cessation. The study results determine Guanfacine to be a pharmacological aid that could be used to control stress from relapse to smoking and help control craving.

Table 3 shows the bias assessment among the studies included for systematic review. According to *Verplaetse et al.*, it is shown from the bias analysis that all the factors included are high-risk bias articles. David S. Mathai *et al.*, the final finding of the article had a low-risk bias. The other articles included in the systematic review had unclear risk, which was not explained clearly.

TABLE 3: BIAS ASSESSMENT OF STUDIES INCLUDED IN OUR SYSTEMATIC REVIEW

Author name, year	Random sequence generation	Allocation concealment	Binding of outcome	Incomplete outcome data	Blinding of participants and personalle	Selective reporting	Judgemental bias
Varplatese *et al*	+	+	+	+	+	+	+
Mathai *et al*	+	-	-	**?**	-	-	-
Sandiego *et al*	+	+	+	-	+	+	**?**
Varplatese *et al*	+	-	-	**?**	-	-	-
McKee *et al*	+	+	-	-	**?**	-	-

DISCUSSION: The topic for discussion regarding this systematic review is the efficacy of Guanfacine as a pharmacological aid to be used by health care providers to persons willing to break free from their addiction in a way to help them fight their craving to smoke. The use of Guanfacine in terms of promoting prefrontal cognition and various other physiological outcomes caused by Guanfacine, such as reduced heart rate and blood pressure, which play a major role in the stress of relapse, craving to smoke, and the number of cigarettes smoked, indicated that the drug could potentially be of great use to break the nicotine addiction that has enslaved thousands of youths worldwide [15]. That being said, Guanfacine may not act directly on the nicotine addiction like the conventional nicotine replacement therapy but will create optimal conditions for an individual willing to break free from the addiction. In the study mentioned above, all the authors have claimed with evidence the effect Guanfacine treatment could potentially have on patients with the addiction problem [16]. In the study piloted by Verplatese *et al.* [10], in the year 2019, it was claimed in the article that this particular study was one of the first to study and juxtapose between the efficacy of 3mg/d of IR Guanfacine, whose effect in the aid for tobacco cessation is known, with that of 4mg/d of ER Guanfacine and 6mg/d of ER Guanfacine if employed as a pharmaceutical aid for tobacco cessation. With a limited sample size of 5, the study was conducted in 3 phases for the different

doses of Guanfacine. The blood samples were obtained, mainly the plasma medication level test, which revealed that the medication level of both 3mg/d IR and four mg/d ER of Guanfacine exhibited almost similar 6mg/d ER of Guanfacine was of different levels. All doses of Guanfacine brought about a notable change in the heart rate blood pressure. The study piloted by Mathai *et al.* [11], in 2017 was to find if Guanfacine would reduce the adverse effects of Dronabinol (THC) on adolescent-onset cannabis users. The limitations involved in this study were attributed to the decreased study period and sample size, thus paving the way for the need to conduct further studies. The authors claim the need to set a dosage that would be the most optimal and serve the purpose.

Furthermore, it should not interfere with the medicinal effects of Dronabinol, which would negate the sole purpose of the study. However, the study supports the fact that Guanfacine would considerably bring down the acute adverse effects of THC on the cognitive function or the PFC function. In conclusion, it is mentioned that Guanfacine could be considered a combination drug to be taken along with THC to promote PFC or Cognitive functions in Heavy cannabis users with adolescent-onset.

The study piloted by Sandiego *et al.* [12], in 2017 was based on the effect that Guanfacine would have on the dopaminergic tone in adult smokers with the help of [11C] FLB457 PET scan. It claimed that the level of dopamine was notably decreased even after induction using amphetamine in Guanfacine-treated patients. Due to the Amphetamine induced dopamine levels after medication of Guanfacine, there was latency in smoking habit also decreased the number of cigarettes was smoked in the time stipulated for self-administration. It was mentioned that the study had its limitations due to the absence of a non-smoking control group. The study piloted by Verplaetse *et al.* [13], in 2017 was totally based on the effects of guanfacine in stress followed by heart rate variability. It claimed that guanfacine has significant benefits for smoking cessation. In clinical trials, regular daily smokers under guanfacine, stress, and HF-HRV were increased compared to daily smokers who were not under Guanfacine. Daily smokers who were not under the treatment of Guanfacine exhibited "blunted" HF-HRV compared to smokers treated with Guanfacine. Clinical results suggest that the HF-HRV rates are inversely proportional to stress and smoking. And it has been discovered in clinical trials that Guanfacine relatively affects the HF-HRV rate fetching a positive outcome. Hence, the trial gives way for further studies on the use of Guanfacine for smoking cessation and a potential pharmacological aid for the same. In the study piloted by McKee *et al.* [14], in the year 2014, the article mentions a case and control study involving 3mg/day Guanfacine and a placebo for the 33 participants associated. It involved taking fMRI of the participants to assess their cognitive function during the laboratory sessions administered. The systolic pressure was markedly reduced post-Guanfacine administration during the titration period, while the diastolic pressure did reduce but without any notable difference. Compared with the Guanfacine group, the placebo group exhibited much less resistance towards their smoke craving.

In contrast, the Guanfacine group displayed decreased stress due to the increased resistance towards their craving. Similarly, the cortisol and ATCH levels also showed notable differences across both the groups, presenting a positive response in Guanfacine administered group of individuals. The administration of 3mg/day of Guanfacine and placebo on participants who were nicotine deprived of the previous night led to a conclusion that the use of Guanfacine in individuals in withdrawal from nicotine can be beneficial as it brings down the stress related to lapse, the urge to smoke as soon as possible and might even let the individual under medication to focus as it improves understanding and cognitive function.

CONCLUSION: In conclusion to this article gauging the efficacy of Guanfacine in treatment for smoking cessation, it could be said that Guanfacine would prove to be a helpful and remarkable Pharmacological aid in smokers. The only limitation to the studies taken into consideration was the limited sample size due to which the effect of the drug could not be assessed vastly but based on the studies; it is vivid that We would like to conclude by stating that Guanfacine could be a pharmaceutical aid of great potential in cases of

smoking cessation and could be included as a part of the treatment plan for smokers by the health care professionals helping them combat their nicotine addiction. The use of Guanfacine on smokers for the cessation of the habit should be studied even more intensely to understand the effects and adverse effects of the drug on smoking individuals.

The study should be done on a larger smoker population to find if the drug has similar effects on different individuals or does it exhibit different effects and adverse effects.

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REFERENCES:

1. Xue T: Associations between exposure to landscape fire smoke and child mortality in low-income and middle-income countries: a matched case-control study. The Lancet Planetary Health 2021; 5(9): 588-98.
2. Kumar S, Kapoor S, Sharma R, Pandey AK and Singh RJ: Compliance assessment with tobacco control regulations at wheelchair-based tobacco Point of sale in Delhi, India. International Journal of Noncommunicable Diseases 2021; 6(1): 38-47.
3. Anu V, Soundharyasri B, Srisruthi P, Madhumithra KG, Sreemadhumitha H and Sornambiga A: Chennai tobacco vendors compliance to India's cigarette and other tobacco products Act (COTPA) 2003 A descriptive evaluation. Indian Journal of Cancer 2021; 58(1): 133-146.
4. Goel S, Kumar R, Lal P, Tripathi JP, Singh RJ, Rathinam A and Christian A: How compliant are tobacco vendors to India's tobacco control legislation on ban of advertisments at point of sale? A three jurisdictions review. Asian Pacific Journal of Cancer Prevention 2015; 15(24): 10637-42.
5. Seth S, Chaturvedi P and Sarin A: Communities against Tobacco (CAT): An important initiative in tobacco control in India. Tobacco Induced Diseases 2021; 19(1): 18-27.
6. Mohan P, Lando HA and Panneer S: Assessment of tobacco consumption and control in India. Indian Journal of Clinical Medicine 2018; 9(2): 11-21.
7. John RM, Sinha P, Munish VG and Tullu FT: Economic Costs of Diseases and Deaths Attributable to Tobacco Use in India, 2017–2018. Nicotine and Tobacco Research 2021; 23(2): 294-301.
8. Kulkarni MM, Kamath VG, Cranwell J, Britton J, Nazar GP, Arora M, Ballal K and Kamath A: Assessment of tobacco imagery and compliance with tobacco-free rules in popular Indian films. Tobacco Cont 2020; 29(1): 119-21.
9. Yadav A, Nazar GP, Rawal T, Arora M, Webster P and Grills N: Plain packaging of tobacco products: the logical next step for tobacco control policy in India. BMJ Global Health 2018; 3(5): 73-81.
10. Verplaetse TL, Roberts W, Moore KE, Peltier MR, Oberleitner LM and McKee SA: Pharmacokinetics and pharmacodynamics of immediate release vs. extended release guanfacine in adult daily smokers. Journal of Clinical Psychopharmacology 2019; 39(2): 124.
11. Mathai DS, Holst M, Rodgman C, Haile CN, Keller J, Hussain MZ, Kosten TR, Newton TF and Verrico CD: Guanfacine attenuates adverse effects of dronabinol (THC) on working memory in adolescent-onset heavy cannabis users: a pilot study. The Journal of Neuropsychiatry and Clinical Neurosciences 2018; 30(1): 66-76.
12. Sandiego CM, Matuskey D, Lavery M, McGovern E, Huang Y, Nabulsi N, Ropchan J, Picciotto MR, Morris ED, McKee SA and Cosgrove KP: The Effect of Treatment with Guanfacine, an Alpha2 Adrenergic Agonist, on Dopaminergic Tone in Tobacco Smokers: An [11 C] FLB457 PET Study. Neurops 2018; 43(5): 1052-8.
13. Verplaetse TL, Smith PH, Smith KM, Oberleitner LM and McKee SA: Guanfacine alters the effect of stress and smoking on heart rate variability in regular daily smokers. Psychopharmacology 2017; 234(5): 805-13.
14. McKee SA, Potenza MN, Kober H, Sofuoglu M, Arnsten AF, Picciotto MR, Weinberger AH, Ashare R and Sinha R: A translational investigation targeting stress-reactivity and prefrontal cognitive control with guanfacine for smoking cessation. J of Psych Oxford, En 2014; 29(3): 300-311.
15. Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, Giovino GA, West R, Hall W, Griffiths P and Ali R: Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction 2018; 113(10): 1905-2196.
16. Quraishi R, Sharma J, Jain R and Ambekar A: Influence of catechol-O-methyltransferase enzyme gene polymorphism on alcohol and tobacco consumption in North Indian treatment seeking population. Indian Journal of Psychiatry 2021; 63(3): 240-248.

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