

Cytisine a New Therapeutic Future for Tobacco Cessation: Short Communication

Rohan Sachdev¹, Kriti Garg², Garima Singh³

^{1,2}Dept of Oral Medicine & Radiology, Rama University, UP, India-208025

³Dept of Pedodontics, Rama University, UP, India-208025

Email address: ²drkriti_garg@rediffmail.com

Abstract— Tobacco in the form of cigarette and chewable leaves are the greatest preventable cause of death in the world. Tobacco use is often incorrectly perceived to be solely a personal choice. Nicotine is the main ingredient in tobacco products available that reinforces individual tobacco addiction behavior; it is tobacco's other components which cause widespread mortality and morbidity. Among treatment available in communities, pharmacotherapeutically cytisine, a natural plant alkaloid derivative from *Cytisus laburnum* is an important upcoming component of efficacious tobacco use interventions.

Keywords— Tobacco; cessation; drug; cytosine; plan.

I. INTRODUCTION

Tobacco and traces of nicotine were discovered in human remains, as early as the prehistoric era, and in Mayan civilization, although there was no clear evidence of the use of tobacco and smoking as a regular activity.¹ Tobacco surely was designed to poison and destroy mankind. Among the countries undergoing epidemiological transition; chronic diseases caused by tobacco are rapidly overtaking the more traditional causes of mortality.² The tobacco epidemic is one of the biggest public health threats the world has ever faced, killing more than 7 million people a year. More than 6 million of those deaths are the result of direct tobacco use³ and tobacco use habit is increasingly being taken up at an early age which is reaching to pandemic levels. Various factors have been implicated for the uptake of the tobacco habit including inadequate knowledge and unfavorable attitude.^{4,5} Adolescents are the most vulnerable population to initiate tobacco use and it is now well established that most of the adult users of tobacco start tobacco use in childhood or adolescence. The World Bank has reported that nearly 82,000-99,000 children and adolescents all over the world begin smoking every day.⁵

Tobacco has nicotine as the main component and dependency of nicotine is the most common substance disorder. Cigarette or tobacco smoking is an addiction, as powerful in many aspects as cocaine dependence and addiction to tobacco smoking results from the binding of nicotine to nicotinic acetylcholine receptors (nAChRs) in the brain, in particular the $\alpha 4\beta 2$ receptor.⁶ Among 4000 chemical compounds of tobacco the alkaloid nicotine is actively present as the primary psychoactive component in tobacco. Nicotine replacement therapies in the form of patch, gum, nasal spray, or inhaler, which diminish drug withdrawal symptoms by providing alternate drug delivery, are the most popular as smoking-cessation aids now a days but these drugs have some disadvantages, like need of frequent dosing, jaw pain, xerostomia, dyspepsia, hiccups, and sometimes sleep disorders. To overcome these disadvantages certain alternative

aid are coming to help in quitting nicotine addiction like cytisine.

Cytisine is an alkaloid from the plant *Laburnum anagyroides* Med, (*Cytisus laburnum*) which is basically distributed in the Sought part of Central and Eastern Europe. All parts of this plant contain the alkaloid cytisine, but the largest quantity (up to 3%) is found in seeds.¹ As per literature available during World War II, the leaves of *Cytisus laburnum* (golden rain tree) were used by smokers as a tobacco substitute.^{7,8} Cytisine has a molecular structure similar to that of nicotine and acetylcholine and it is an agonist of nicotinic receptors; in particular, cytisine has a high affinity for nicotinic receptors. In 1978, the tobacco industry identified cytisine as the substance with the pharmacological action closest to that of nicotine. Because of its affinity to nicotinic receptors and its pharmacological similarities to nicotine, cytisine is being used as a starting material for the development of new drugs.⁹

Role of Cytisine

Cytisine is a compound derived from the plant, *Cytisus laburnum*. It is a nicotinic partial agonist binding with high affinity to a number of different subtypes of the neuronal nicotinic receptors, including receptors composed of $\alpha 4$ and $\beta 2$ subunits which are believed to be central to the effect of nicotine on the reward pathway. Because it has a high affinity for the receptor, cytisine prevents other ligands such as nicotine from attaching to it¹⁰, however, once attached to the receptor; its effect is much less than that of nicotine. This drug interaction may cause reduction in the rewarding effects of nicotine and to decrease craving and attenuate nicotine withdrawal symptoms, but not be addictive itself or provide positive effect.^{11,12}

Drug cytisine has a lower toxicity than nicotine and weaker peripheral effects on cardiovascular system. As per studies performed cytisine could be used as an alternative to nicotine – replacement therapy.¹³ Cytisine, a partial nicotinic acetylcholine receptor agonist, have been shown to exert neuroprotective actions in vivo and in vitro by an as yet unknown mechanism. It was suggested that neuroprotection

was mediated through the $\alpha 7$ nicotinic receptor subtype.¹⁴ Pharmacologically cytisine is almost similar to nicotine. Cytisine found to be more effective than nicotine in increasing [3H]-norepinephrine release, and has a similar to nicotine effect on [3H]-dopamine release.¹⁵ Cytisine, like nicotine act on dopaminergic neurotransmission and stimulate dopamine release in brain, but the involvement of dopamine release in the cognitive effects of nAChR activation is yet not clear.¹⁶ Cytisine is an agonist of cholinergic receptors in the vegetative ganglia which may lead to bradycardia and excitation of the respiratory center. Cytisine may produce toxicity in gastrointestinal tract, nausea, vomiting may start 45 minutes to 4 hours after ingestion of the drug.¹⁷ CNS effect include drowsiness, weakness and loss of coordination, muscle fasciculation, seizures, coma and mydriasis.^{1,16,18} Cytisine is a generic agent currently manufactured by Sopharma as Tabex and by Aflofarm Pharma as Desmoxan. The drug dosing for cytisine was established in the 1960s, but the rationale for the dosing schedule is unclear. Patients can be asked to take six 1.5 mg tablets, one every 2 h, over the first 3 days and to stop smoking by day 3, which is followed by five tablets daily for days 4–12 (one tablet every 2.5 h), four tablets for days 13–16 (every 3 h), three tablets for days 17–20 (every 4 h) and two tablets for days 21–25 (every 6 h), totaling of 100 tablets.¹⁷ It has been available both with and without prescription for smoking cessation.¹⁹

II. CONCLUSION

Cytisine, medication developed in Eastern Europe from last 40 years as an aid to smoking cessation, appears to improve abstinence rates in smokers attempting to stop. Cytisine was superior to nicotine-replacement therapy for smoking cessation because of less side effects among dependent smokers motivated to quit. Existing literature, on cytisine as a smoking cessation aid have suggested that the drug is efficacious and safe; however, these studies do not conform to modern standards in conducting and reporting drug trials, and should be interpreted with caution. Since cytisine exhibits a desirable *in vitro* and *in vivo* profile, it should be advanced to randomized controlled trials. Before that, more information on its pharmacokinetics and safety profile in humans for dosages recommended by the manufacturer is required.

REFERENCES

- [1] Tzankova V, Danchev N. Cytisine—from Ethomedical use to the Development as a Natural Alternative for Smoking Cessation. *Biotechnology & Biotechnological Equipment* 2007;21(2): 151-160.
- [2] <http://www.who.int/news-room/fact-sheets/detail/tobacco>
- [3] Ballal K, Kulkarni M, Agrawal A, Kamath A, Kumar M. Knowledge and attitude regarding tobacco and its use among adolescent students. *Ntl J Community Med* 2016; 7(6):519-523.
- [4] Chadda RK, Sengupta SN. Tobacco use by Indian adolescents. *Tobacco Induced Diseases* 2002; 1(2): 111–119.
- [5] Rucktooa P, Haseler CA, Elk R, Smit AB, Gallagher T, Sixma TK. Structural characterization of the binding mode of smoking cessation drugs to nicotinic acetylcholine receptors through the study of ligand complexes with acetylcholine binding protein. <http://www.jbc.org/cgi/doi/10.1074/jbc.M112.360347>
- [6] Etter JE. Cytisine for Smoking Cessation A Literature Review and a Meta-analysis. *Arch Intern Med.* 2006;166:1553-1559.
- [7] https://www.lareb.nl/media/3070/signals_2017_tabex_psychosis.pdf
- [8] Zatoński W, Cedzyska M, Tutka P, West R. An uncontrolled trial of cytisine (Tabex) for smoking cessation. *Tobacco Control* 2006;15:481–484.
- [9] Imming P, Klaperski P, Stubbs MT, Seitz G, Gundisch D. Syntheses and evaluation of halogenated cytisine derivatives and of bioisosteric thiocytisine as potent and selective nAChR ligands. *Eur J Med Chem.* 2001;36:375-388.
- [10] Gopalakrishnan M, Monteggia LM, Anderson DJ, et al. Stable expression, pharmacologic properties and regulation of the human neuronal nicotinic acetylcholine $\alpha 4 \beta 2$ receptor. *J Pharmacol Exp Ther* 1996;276:289–97.
- [11] Walker N. Cytisine versus Nicotine for Smoking Cessation. *N Engl J Med* 2014; 371(25):2353-2362.
- [12] West R. Placebo-Controlled Trial of Cytisine for Smoking Cessation. *N Engl J Med* 2011;365(13):1193-1200.
- [13] Jonnala R.R., Buccafusco J.J. Nicotinic ACh Receptors in the Hippocampus: Role in Excitability and Plasticity. *Journal of Neuroscience Research* 2001;66:565-572.
- [14] Brioni J.D., Americ S.P. Nicotinic receptor agonists facilitate retention of avoidance training: participation of dopaminergic mechanisms. *Behavioral and Neural Biology* 1993;59:57-62.
- [15] Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. *Pharmacol Rep.* 2006;58(6):777-98.
- [16] Schulters RE. (1970) *Annual Review of Plant Physiology and Plant Molecular Biology*, 21, 571. <https://www.annualreviews.org/doi/abs/10.1146/annurev.pp.21.060170.03035>
- [17] Hajek P, McRobbie H, Myers K. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. *Thorax* 2013;1–6.
- [18] Howick J. Truth about stop smoking drug ‘cytisine’ beats conspiracies. <http://www.jeremyhowick.com/latest-updates/truth-stop-smoking-drug-cytisine-beats-conspiracies/>
- [19] Gross N.A. Drug Better Than Nicotine for Smoking Cessation? https://www.medscape.com/viewarticle/838496?src=trendmd_pilot