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Review Article

Nicotine Replacement Therapy: A Successful Quit Attempt for Tobacco

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Abstract

In an effort to help smokers stop, Nicotine Replacement Therapy (NRT) delivers regulated, low doses of nicotine to reduce cravings and withdrawal symptoms. Five different NRT patch, gum, nasal spray, inhaler, and lozenge forms have been approved by the FDA, allowing people to select the one that best suits their needs. NRTs effectiveness in helping people quit smoking is supported by a large body of research that addresses both the psychological and physiological components of addiction. Since quitting frequently takes numerous efforts, combining NRT with behavioural counselling and support programmes increases the likelihood of success. Alternative techniques to treating drug addiction are provided by Ayurvedic, Siddha, and Unani therapies, which place an emphasis on individualized care and holistic wellbeing. These traditional systems include Panchakarma rites, Rasayana therapies, and herbal formulations as essential elements. Yoga therapy is a unique kind of rehabilitation that helps those overcoming from drug addiction by increasing the production of endorphins and improving mental clarity. Pharmacological therapies have been shown to be beneficial in lowering cravings and withdrawal symptoms. These interventions include first-line drugs such as Varenicline and Bupropion. The second-line treatments are cytisine and nortriptyline, while the latter may have adverse effects. Combination medicines have demonstrated enhanced efficacy in helping people stop smoking; however, possible adverse effects and financial considerations must be taken into account. Examples of these combinations include using a nicotine patch in conjunction with short-acting NRT or varenicline and bupropion. While the effectiveness of some treatments, such as clonidine and selective serotonin reuptake inhibitors/anxiolytics, has been demonstrated to some extent, other treatments, such as nicotine vaccine and electronic cigarettes, are still being studied.

INTRODUCTION

As the main alkaloid in tobacco smoke and a highly addictive chemical molecule present in tobacco plants, nicotine is essential in regulating the psychopharmacological effects linked to addiction (Foulds, *et al.,* 2004; Cherer, *et al.,*1999). The problem of nicotine addiction continues to be a major global public health issue, adding considerably to the burden of chronic illnesses (Ncbi, 2006). The nicotine concentration of tobacco products is what makes them addicting. As a result, the body adjusts to the occurrence of nicotine in different regions when a person smokes. When people stop using tobacco products, they also stop using nicotine, which causes withdrawal symptoms. This happens as a result of the body having to adjust to not having nicotine (2011; Engl, 2010). By using devices that deliver controlled, low levels of nicotine, NRT is a cessation strategy intended to help people stop smoking. The principal aim of this treatment is to reduce nicotine cravings and mitigate the symptoms related to nicotine withdrawal (Silagy, 2004).

By administering nicotine in different forms, NRT works to lessen the desire to smoke as well as the physical and psychological symptoms of withdrawal (Wadgave, 2016).

Notably, five distinct types of replacement nicotine therapy have been approved by the food and Drug Ministry (Patch, Gum, Nasal spray, Inhalers and Lozenges) (Schnoll *et al.,* 2015).Several studies demonstrate how well NRT works to help people stop smoking. NRT lessens the symptoms of withdrawal by administering nicotine in a regulated way, making it easier for people to escape the cycle of addiction. Moreover, NRT tackles the psychological aspects of smoking by offering alternatives to the ritualistic behaviors connected to tobacco use. NRT's versatility, which provides a range of formulas to suit individual preferences, is one of its main advantages. NRT enables a customized approach to smoking cessation, regardless of the preference for the inconspicuousness of a patch, the oral gratification of gum, or the inhaling aspect of an inhaler (Pollak KI, *et al.,* 2007). Although long-term use of nicotine patches is thought to be safe, studies suggest that their usefulness could not last more than 24 weeks for a variety of smokers (**Jiloha, 2014**). As a component of a thorough smoking cessation programme that incorporates behavioral counseling and support, NRT is frequently advised (Sandhu 2023). By treating the physiological and psychological elements of addiction, the combination of pharmaceutical treatments and behavioral techniques increases the chances of a successful cessation (**Yildiz, 2004**).

While some people can effectively stop using tobacco products without the help of NRT, many people who try to stop typically fail and need to try several times before they can stop permanently. The difficulty is further highlighted by the fact that many people who try to stop on their own usually relapse within the first month, mostly as a result of withdrawal symptoms. In spite of this, there is good news: a sizable portion of people succeed in quitting, meaning that there are now more former smokers than present. While some individuals can successfully quit smoking tobacco products without the assistance of NRT many others who attempt to quit usually are unsuccessful and require multiple attempts before they are able to quit for good. The fact that many individuals who attempt to quit on their own typically relapse within the first month, primarily due to withdrawal symptoms, emphasizes the challenge even more. Despite this, there is good news: a significant number of people are successful in stopping, which means that the number of former smokers has surpassed the current number (Narahashi, *et al.,* 2000). It's crucial to remember that NRT just treats the physical dependence issue and shouldn't be the only strategy used to stop smoking. It is advised to combine NRT with techniques like a quit programme that treat the psychological components of tobacco addiction. It has been demonstrated that, in comparison to approaches that rely solely on one strategy, employing support networks both throughout NRT therapy and for a few months following quitting increases the likelihood of a successful cessation. When it comes to the best time to begin NRT, it is advised to begin immediately after making the decision to stop smoking, as opposed to waiting until one or more days into the quitting process. It could take several tries to succeed, but people are urged not to give up. It's crucial to remember that although the FDA has recognized NRT products as useful tools for quitting smoking, none of these medications have been approved by the FDA expressly for helping people stop using smokeless tobacco. Studies in this area are still being carried out, some of which hint at the lozenge forms possible benefits (Tiwari, *et al.,*2020). Nicotine replacement therapy (NRT) is effective in treating difficult cravings and withdrawal symptoms, which are typically recognized as the main barriers to quitting tobacco. It has been demonstrated that using NRT successfully reduces these symptoms (Pandit, 2023).

Mechanism of Action of Nicotine

The main psychotropic ingredient in tobacco is nicotine. The lungs or oral mucosa allow nicotine to enter the bloodstream when a person smokes a cigarette or consumes tobacco in other ways (such as chewing tobacco or vaping).

Nicotine attaches itself to brain nicotinic acetylcholine receptors, or nAChRs. These receptors are present in the mesolimbic pathway and other regions linked to pleasure and reward. Dopamine, acetylcholine, norepinephrine, serotonine, vasopressin, beta-endorphin, and ACTH are released in greater amounts when nicotine activates nAChRs a neurotransmitter essential to motivation, pleasure, and reinforcement. The desire to consume nicotine is increased by the dopamine surge, which produces sensations of pleasure and euphoria.

The reward system in the brain changes when nicotine is ingested repeatedly. With time, the brain's natural production of dopamine may decline along with the amount of nAChRs. Tolerance develops as a result, requiring higher doses of

nicotine to produce the same enjoyable benefits (West, *et al.,* 2017).

Ayurvedic Remedies for Drug Addiction

Giving up tobacco usage becomes crucial for both preventing and curing numerous ailments because Ayurveda believes that treating any illness requires removing its underlying cause (Rao, *et al.,*2022). However, preventing this cause, uncontrolled tobacco addiction remains a challenge. Over a billion people are thought to smoke regularly worldwide, despite being aware of the negative repercussions of doing so.

Various Ayurvedic remedies for drug addiction:

Panchakarma

Making ensuring that Panchakarma treatments or rituals are only carried out by Ayurvedic experts is the most important factor. Panchakarma, an Ayurvedic therapy, helps the body detoxify. Utilizing a variety of oils and herbs in accordance with traditional practices and procedures from ancient times, this process aids in the removal of bad circumstances (Rao, *et al.,*2022; Ravishankar, *et al.,*2007).

Various types of oils and herbs

Triphala: Because of its purifying and revitalising qualities, triphala, a concoction of three fruits is frequently employed in Panchakarma. These fruits include amla, harithi, and bibhitaki. It aids in cleansing and digestion. ***Guggul****:* is used to enhance the body's removal of toxins and to help balance the doshas. In Panchakarma, it is frequently used to encourage detoxification.

Neem: is well-known for having purifying and antimicrobial qualities. It aids in the body's cleansing during a variety of Panchakarma treatments. ***Trikatu****:* is a remedy used to boost metabolism and digestion that combines three strong herbs: long pepper, black pepper, and ginger. It frequently occurs during Panchakarma preparations. ***Aloe-vera:*** is utilised in some Panchakarma therapies and is used for its calming and cooling qualities. ***Bilva*** (Bael): Panchakarma uses bilva leaves and fruit because of its cleansing and digestive qualities.

Musta: Because of its ability to aid in detoxifying and digesting, musta is utilised in Panchakarma. ***Bhringaraj:*** for therapies like Abhyanga (oil massage) and Shirodhara (application of herbal oil to the forehead), bhringaraj is utilised in herbal oils and pastes.

Shatavari: can be found in formulations and is frequently utilised during Panchakarma to support the body's general health.

Virechana

Virechana, one of the more powerful Panchakarma therapies, is well known for its exceptional efficacy in treating drug addiction. Through the removal of toxins, vivechana helps to cleanse the gastrointestinal system and purify the blood. Virechana aids in the decontamination of the spleen, liver, kidney, stomach, colon, intestine, and sweat glands, among other organs and systems. Herbs and oils, in particular castor oil, mango juice, cow's milk, raisins, psyllium seeds, husk of flax seeds, senna, and prune, are used in vivechana therapy (Kumar, 2020).

Rasayana Therapies

Rasayana treatments are another very successful Ayurvedic treatment for drug addiction and abuse. Rasayana therapy mainly uses the concepts of energy conservation and transmutation to improve mental and physical qualities. The intention is to boost immune system and brain function as well as the body's natural metabolic processes. Massages on the face, head, and entire body using medicinal oils and herbal creams are among the Rasayana therapies. This treatment is helpful in treating the problem of artificial ageing brought on by long-term drug misuse (Balasubramani, 2011; Rathi, 2020).

Siddha Remedies for Drug Addiction

Tobacco addiction has long been treated using herbal compositions according to the siddha medical system. The formulation "Noolvayu Kudineer" is one example. It is thought that the ingredients in this formulation may help lessen withdrawal symptoms and cravings for tobacco. It's crucial to remember that each person may respond differently to these herbal formulations, and there may not be enough scientific data to support their usage in the treatment of addiction (Selvasankari,2022). Herbs and substances that may be used in siddha formulations for tobacco addiction:

Acalyphaindica (Kuppaimeni): well known for its ability to lessen tobacco cravings.

Piper betle (Vetrilai): thought to possess anti-addictive qualities and could aid in lowering the craving for smoke.

Zingiberofficinale (Sukku): used due of its ability to lessen the symptoms of withdrawal.

Terminalia chebula (Kadukkai): Given its digestive and cleansing qualities, it might be added.

Terminalia bellirica (Thandrikkai): utilised because of its capacity to enhance general health during healing.

Emblicaofficinalis (Nellikkai): renowned for having antioxidant qualities that may aid in detoxification (Selvasankari,2022; 2019).

Unani Remedies for Drug Addiction

With its all-encompassing approach to health and wellbeing, unani medicine might provide nicotine addiction treatment choices. Here are some broad guidelines and herbs that may be taken into consideration in the Unani system of managing nicotine addiction, even if the precise drugs and therapies recommended by Unani practitioners can differ based on individual characteristics (Sofi, 2023).

Herbal Formulations: Herbal treatments play a significant role in unani medicine. It is possible to lessen withdrawal symptoms and cravings for nicotine by using specific herbs. Herbs that are used to help with addiction include Brahmi (Bacopamonnieri), Shankhpushpi (Convolvulus pluricaulis), and Jatamansi (Nardostachysjatamansi) (Selvasankari, 2022).

Detoxification (Tadbeer): To help the body get rid of pollutants, Unani emphasises detoxification techniques. This could involve changing one's diet and using some herbal supplements to help the body detoxify from nicotine and associated chemicals.

Dietary and Lifestyle Changes: Nutritional adjustments and lifestyle adjustments are frequently suggested by unani practitioners to aid in the healing process. The comprehensive approach may include stress management strategies, a healthy diet, and frequent exercise (Sofi, 2023).

Counseling and Behavioral Therapy: The field of unani medicine recognises the significance of treating the psychological components of addiction. To assist people in overcoming cravings and triggers, some practitioners may combine behavioural therapy and counselling strategies.

Personalized Treatment: Treatment regimens in unani medicine are customised based on each patient's distinct constitution (Mizaj) and general state of health. From person to person, different Unani prescriptions and formulations may be used (Sofi, 2023).

Yoga

Drug abusers who receive yoga treatment can recover well (Mathew *et al.,* 2013). Drug abusers' brains are known to be significantly impacted by the chemicals in their substances during the recovery period. An addict might increase their brain's production of "endorphin chemicals" (Jan, 2015) by practicing yoga and other physical activities. This can significantly help them achieve mental clarity. In addition to obtaining Ayurvedic therapy, an addict may want to think about enrolling in a structured yoga programme to help them fully recover from their drug addiction (Woodyard, 2011). Since yoga stimulates all of the body's organs without overstressing any one of them, it is equally beneficial and particularly helpful for beating drug addiction (Kuppili, 2018).

Five types of nicotine replacement therapy (NRT) have been approved by the US Food and Drug Administration (FDA): patches, gum, nasal sprays, inhalers, and lozenges.

Table1. NRT and its dosage (Moerke, 2020**;** Shiffman, 2003; Digard, 2013; Barua *et al.,* 2018; 2020**).**

Types of NRT	**Available Dosage**
Lozenges	1mg, 2 mg and 4 mg .
Gum	2 mg and 4 mg.
Patch	5 mg, 10 mg, 15 mg doses worn over 16 hours 7 mg, 14 mg, 21 mg doses worn over 24 hours.
Nasal spray	0.5mg dose/spray.
Inhalers	10 mg cartridge delivers 4 mg inhaled vapor.

Table 2. Mechanism of action of NRT (Moerke, 2020; Shiffman, 2003; Digard, 2013, Barua *et al.,* 2018; 2020).

Types	**Absorption**	**Binding**	**Dopamine release**	**Gradual reduction**
Lozenges	Oral Absorption through the mucous membranes of the mouth and throat. And reaches into bloodstream.	Nicotinic acetylcholine receptors (nAChRs)	Activation of nAChRs by nicotine leads to the release of neurotransmitters, particularly dopamine. Dopamine is associated with feelings of pleasure and reward, which can help to reduce withdrawal symptoms and cravings associated with quitting smoking.	starting with a higher-dose and then gradually moving to lower-dose over time.
Gum				
Patch	Absorption by transdermal delivery. And reaches into bloodstream.			
Nasal spray	Absorption by nasal passages.			
Inhalers	Absorption through the oral mucous			

Currently Available Medications

Varenicline by binding to the alpha-4beta-2nicotinic receptor with high affinity and functioning as a partial agonist, varenicline lessens the symptoms associated with nicotine withdrawal. By preventing nicotine from attaching to the receptor, it prevents the addictive properties of nicotine that cause dependency. Varenicline lessens the warding effects of smoking cigarettes by doing this. By increasing the receptor's activity, it also lessens cravings and withdrawal (Coe, 2005).

Mechanism of Action: Because of its dual agonist antagonist activity, an α4β2nAChR partial agonist may have a lower abuse liability than nicotine, while still improving abstinence rates when compared to NRT. α4β2nAChRs mediate the addictive qualities of nicotine (Brunzell,2012). One of the reasons vannicline was chosen for development was its strong affinity for α4β2 nAChRs. A high affinity partial agonist at α4β2 containing (α6β2) nAChRs, which are also important in nicotine dependence, was later demonstrated to be present (Ollema, 2007).The preclinical in vivo profile of vannicline is similar to that of a partial agonist of α4β2/α6β2. It decreases nicotine self-administration, reduces nicotine-induced dopamine release, and increases basal mesolimbic dopamine release to about 50% of the maximal impact of nicotine (Warner, 2005; Paccosi, 2020).

Bupropion it is thought that bupropion works by increasing dopaminergic and noradrenergic release in the central nervous system. Bupropion has been demonstrated to oppose nicotinic acetylcholine receptor activity in addition to being a mild inhibitor of dopamine and noradrenaline reuptake. In humans, it undergoes substantial metabolism, with its main metabolites reaching levels greater than those of bupropion (Jefferson, 2005).

Mechanism of Action: Bupropion is an aminoketone antidepressant whose precise mode of action is uncertain (Connarn, 2015). Bupropion does not appear to affect monoamine uptake, however it is known to somewhat impair the absorption of dopamine and norepinephrine. It appears that the effects on norepinephrine and dopamine are what lead to the clinical symptoms. Norepinephrine uptake is said to be less potent than dopamine absorption inhibition. Furthermore, bupropion's impact on nicotinic and serotonin receptors is lessened. Bupropion typically starts to have a therapeutic impact around the second week of treatment. The maximum concentration of serum occurs after two hours for instantaneous release, three hours for prolonged release, and five hours for extended release. The activity lasts for one to two days. Bupropion is rapidly absorbed by the gastrointestinal (GI) tract, with a volume of distribution ranging from around 20 L/kg to 47 L/kg. Protein binding will account for 84% of the drug's composition CYP2B6 breaks down bupropion in the liver to produce hydroxybupropion. Erythrohydrobupropion and threohydrobupropion are the products of non-CYP metabolism. These metabolites have 20–50% of the original compound's potency, making them active. At last, a glycinated conjugate is formed, which is then eliminated by the kidneys.

Eighty-seven percent of the medication is eliminated in the urine, and ten percent in the faeces (Connarn, 2015). Bupropion has a half-life of three to four hours in dispersion, but when taken regularly, the half-life rises to approximately twenty-one hours.

Cytisine Similar to varenicline, cytisine also referred to as cytisinicline in the US; is a plant derivative that partially agonistically activates the alpha-4 beta-2 nicotinic acetylcholine receptor (Hays, 2008). Compared to placebo and single-agent NRTA, it seems to be more efficacious. When accessible, cytisine is an acceptable option for quitting smoking and could provide a less expensive pharmacologic alternative to treatments like varenicline. Cytisine has been used for decades to help people stop smoking in Eastern Europe, but it is not available in the US or Western Europe since the US FDA or its European equivalent have not yet studied it (Karnieg, 2018).

Mechanism of Action: An alkaloid used to help people quit smoking is called cytisine. It has partial agonist activity at the α4β2 nicotinic acetylcholine receptor. A partial agonist with poor effectiveness for nicotinic acetylcholine receptors β4-β2 is cytisine. These are thought to be essential to nicotine's (NIC) impact on the reward system and ability to promote addiction. When taken alone, cytisine lessens the effects of NIC on dopamine release in the mesolimbic system while also lessening the symptoms of NIC withdrawal that come with trying to stop (Livingstone, 2023; Walker, 2014; Rigotti, 2023; Rigotti 2014; Zatoński, 2015).

Nortriptyline Tricyclic antidepressant nortriptyline is a second-line treatment that has demonstrated a modest level of success in helping smokers stop for those who are unable to utilise a Ist medication or who require an adjuvant to Ist therapy. It raised the chance of abstinence compared with placebo in a meta-analysis of six studies and 975 people (Hajizadeh, 2023; Wagena, 2005; Prochazka, 1998; Hall, 2002; Hall, 1998) (RR 2.03, 95% CI 1.48-2.78). But nortriptyline users were more likely to experience drowsiness and dry mouth as side effects.

Mechanism of Action: Tricyclics (secondary amines), or TCAs for short, are a class of pharmacological substances that includes the antidepressant nortriptyline. Most agree that nortriptyline increases the concentration of those neurotransmitters in the synapse by preventing the presynaptic neuronal membrane from reabsorbing serotonin and norepinephrine. Nortriptyline also prevents histamine, 5-hydroxytryptamine, and acetylcholine from acting. Nortriptyline inhibits phenethylamine's pressure response while amplifying norepinephrine's pressor impact. Nevertheless, studies have also discovered other impacts of receptors, such as down-regulation of serotonin receptors, desensitization of adenylyl cyclase, and down-regulation of beta-adrenergic receptors.The proposed mechanism of action of nortryptyline in neuropathic pain is an increase in noradrenaline levels acting inside dorsal root ganglia on β2-adrenoceptors generated by non-neuronal satellite cells. Neuropathic pain is alleviated as a result of this stimulation of β2-adrenoreceptors, which lowers the generation of TNFα brought on by neuropathy (Bohren, 2013). While the precise method by which nortriptyline aids in smoking cessation remains unclear, it could function by emulating the effects of nicotine on the noradrenergic system.

Although more investigation is necessary, a recent study suggests that nortriptyline may be a helpful new antimicrobial treatment against infections of Candida albicans that are resistant to drugs because it efficiently suppresses biofilm and kills cells in a grown biofilm (Gomez-Coronado, 2018; Szegedi, 2009). Even though the antidepressant effect takes a few weeks to manifest, peak plasma concentrations occur 7 to 8.5 hours after oral dosing. The liver, heart, and brain get nortriptyline. Tissue proteins and plasma are strongly attached to nortriptyline and its metabolite. Breast milk contains nortriptyline as well as the drug passes the placenta. When taken orally, nortriptyline is metabolised by CYP2D6 in the liver in the first pass (Hicks, 2017). Urine release, which excretes around one-third of the dose as metabolites in a day, is the primary mode of elimination. The drug is also expelled by bile as stool.

Therapies with limited or unproven benefit

Clonidine is currently generally considered to have little efficacy for smoking cessation, despite encouraging initial research (Prochazka, 1992). While a meta-analysis revealed that clonidine was more effective than a placebo in helping people quit smoking, most individual studies assessing the medication have not shown statistically significant efficacy. The utility of clonidine as a smoking cessation aid is further limited by adverse effects, which include weariness, sleepiness, and dry mouth.

Mechanism of Action: An imidazoline derivative called clonidine hydrochloride functions as an agonist on the alpha-2 adrenergic centrally.

2-((2,6-dichlorophenyl) amino)-2-imidazoline hydrochloride is the chemical name for clonidine. As an alpha-adrenergic agonist, clonidine activates an enzyme in the nucleus tractus solitarii (NTS) that suppresses excitation cardiovascular neurons. Both the posterior hypothalamus and the medulla respond to clonidine as an alpha-antagonist. The ultimate result is decreased sympathetic outflow from the central nervous system (CNS), which lowers arterial blood pressure in a way that is clinically significant. Clonidine stimulates a pathway in the nucleus tractus solitarii (NTS) that suppresses excitatory cardiovascular neurons, acting as an alpha-adrenergic agonist. Clonidine acts as an alpha-antagonist in the medulla and posterior hypothalamus. Reduced sympathetic outflow from the central nervous system (CNS) is the ultimate response, and this reduces arterial blood pressure in a clinically meaningful way. When used in conjunction with local anaesthetics, epidural clonidine acts through three distinct methods. Firstly, pain transmission is decreased when alpha-2-receptors in the dorsal horn are stimulated. Second, local vasoconstriction brought on by clonidine may restrict the circulatory clearance of local epidural anaesthetics. Last but not least, clonidine improves neuraxial opioids and interacts additively with fentanyl to reduce the dose of each drug by 60% for postoperative analgesia.

Clonidines precise mode of action in treating attention-deficit hyperactivity disorder (ADHD) is unknown; however it's probable that prefrontal cortex activity plays a role (Prochazka,1992).

Selective serotonin reuptake inhibitors/anxiolytics calming agents It has generally not been demonstrated that anxiolytic medications and selective serotonin reuptake inhibitors (SSRIs) are helpful in helping people stop smoking (Covey, 2000).

Nicotine vaccine The creation of a nicotine vaccine is one novel experimental strategy for the treatment of tobacco dependence. Theoretically, the immunization would result in the production of antinicotine antibodies, which would prevent nicotine from binding to nicotine receptors in the central nervous system and lessen the enjoyable pleasure of smoking (Hartmann-Boyce, 2012; Carrera, 2004).

Electronic cigarettes also referred to as e-cigarettes, are nicotine delivery devices that run on batteries. Different e-cigarette products with varying nicotine delivery times and quantities are available in the market. Because the tobacco is not burned, these devices are likely safer than continue to smoke regular tobacco cigarettes. However, it's unknown if using them in the long run will be safe. The US Food and Drug Administration (FDA) have approved some e-cigarette devices as tobacco products that can be sold as consumer goods since their overall benefits outweigh their drawbacks for the general public. Nevertheless, the FDA has not assessed or authorized any e-cigarette as a medicinal product for quitting smoking (LeSage, 2006).

Combination of NRT

Because each nicotine replacement medication delivers a lower blood nicotine level than smoking one pack of cigarettes per day, it is safe to combine them. Combination NRT combines the long-acting nicotine patch with a patient-selected short-acting NRT (such as nicotine gum or lozenges) (Smith, 2009). For a full day, the patch relieves withdrawal symptoms consistently. The "as needed" addition of the short-acting nicotine medication helps manage breakthrough cravings and other withdrawal symptoms. Combination NRT is better than single-type NRT while using NRT because of its increased effectiveness. Research indicates that NRT is a successful smoking cessation strategy. Combination therapy with both long- and short-acting formulations is recommended for those who want to utilize NRT. NRT drugs individually outperform placebos, with up to a twofold increase in quit rates. Any kind of NRT produced higher abstinence rates than placebo (16 versus 10.5 percent, respectively; RR 1.55; 95% CI 1.49-1.61) in a meta-analysis of 133 trials including 64,640 people.

The majority of trial data indicate that using a long-acting patch alone is not as beneficial as using it in combination with a short-acting medication, like gum, lozenges, or inhalers. The use of a nicotine patch in conjunction with a short-acting NRT product (gum, spray, or inhaler) was found to be more successful than using just one kind of NRT (relative risk 1.25, 95% CI 1.15-1.36) in a meta-analysis of 14 randomized studies. In other trials, combination NRT proved to be more successful than single-product treatments. Nonetheless, no differences were observed in the biochemically validated rates of smoking abstinence between the nicotine patch and combination NRT (nicotine patch with lozenge) in a randomized experiment involving 1086 smokers (Baker,2021).

Combination pharmacotherapy

Although pharmacological combinations seem to be more successful than monotherapy, they are also more costly and may result in more side effects. Combination therapy makes sense for people whose

first drugs only partially improved their condition. Research backs up the use of varenicline and nicotine patches together.

Varenicline and nicotine patch There may be more adverse reactions, even if varenicline plus nicotine patch may be a superior combination for quitting smoking than varenicline alone (Baker,2021). At a six-month follow-up, therapy with varenicline plus nicotine patch for 12 weeks resulted in higher rates of continuous abstinence (49 versus 33 percent; odds Ratio [OR] 1.98, 95% CI 1.25-3.14) in a randomized study involving 435 smokers (Piper, 2009). For individuals using both medications, there was a little but not significant rise in adverse effects, such as nausea, constipation, and sleep disturbances. Conversely, a similar trial with 1251 participants found similar abstention rates with monotherapy compared to combined varenicline with nicotine patch at the 52-week follow-up (Baker,2016; Koegelenberg, 2014).

Bupropion and varenicline Varenicline may be a more effective smoking cessation drug when paired with bupropion than when used alone A meta-analysis (four studies; 1057 participants) found a nonsignificant tendency towards higher smoking cessation rates for those on combination bupropion and varenicline therapy compared to varenicline alone.

Bupropion and NRT A combination of NRT and sustained-release bupropion resulted in greater rates of abstinence than NRT alone (relative risk 1.17, CI 0.95-1.44), according to a meta-analysis of 15 randomised studies (Ebbert, 2014). This trend was not statistically significant.

Nortriptyline and NRT In comparison to NRT alone, adding nortriptyline to NRT (four trials) in a meta-analysis revealed a trend towards greater rates of abstinence (risk ratio 1.21, CI 0.94-1.55). This outcome is comparable to what was discovered when bupropion was added to NRT (Ebbert, 2014).

Conclusion

Overcoming nicotine addiction necessitates a careful and comprehensive strategy. While some treatments, including as Nicotine Replacement Therapy, can help reduce the physical cravings, long-term success requires combining these treatments with counseling and support. In addition to conventional medicine, investigating alternative therapies such as Ayurveda and implementing lifestyle modifications like yoga might enhance a more comprehensive approach. Varenicline and bupropion are examples of helpful medications, and experimenting with different treatment combinations may increase their efficacy. Though they may appear to be a safer option, e-cigarettes' long-term safety is still unknown. Nicotine vaccines are one example of an experimental treatment that shows potential in altering the rewarding nature of smoking. Making lifestyle changes and establishing robust support networks, including as counseling, are essential for a successful quit attempt. Further research on the effects of Avurveda, Siddha, and Unani in drug addiction and tobacco dependency is necessary because these treatments have no negative side effects.

Author Declaration

We certify that each of the listed authors has read and approved the article, and that no other persons meet the requirements to be included as authors. We also certify that we have all approved the order of authors as stated in the manuscript.

Declaration of competing Interest

All authors declare no conflict of interest.

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