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Non-Nicotinic–Based Therapies for Smoking Cessation

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Abstract: *Because smoking is linked to cardiovascular, pulmonary, neurological, and cancerous conditions, it continues to be a major global public health problem and causes millions of avoidable deaths annually. The investigation of non-nicotinic treatment methods has been prompted by the limits of nicotine replacement therapies (NRTs), despite their widespread use for smoking cessation. These drawbacks include inadequate withdrawal alleviation, poor adherence, side effects, and relapse among highly dependent smokers. This review article addresses the mechanics, efficacy, safety, and future prospects of non-nicotinic-based smoking cessation therapy. The potential of pharmacological treatments such as bupropion, varenicline, nortriptyline, cannabinoid receptor modulators, nicotine vaccines, and glutamatergic drugs to target neuronal pathways other than nicotinic receptors is investigated. The effectiveness of non-pharmacological treatments including digital therapies, counselling, cognitive behavioural therapy, mindfulness-based therapy, and neuromodulatory methods like repeated transcranial magnetic stimulation in lowering cravings and relapse is also assessed. The neuroscience of nicotine addiction including the dopaminergic, serotonergic, and glutamatergic systems—all of which provide crucial targets for cutting-edge treatments—is also highlighted in the paper. The study also lists the short follow-up period, methodological heterogeneity, and insufficient representation of varied communities as current research shortcomings. Everything aside, non-nicotinic therapies exhibit tremendous potential as extra or alternative approaches for smoking cessation, and they may greatly enhance long-term abstinence rates and reduce the burden of tobacco addiction internationally.*

Keywords: Smoking Cessation, Non-Nicotinic Therapy, Nicotine Addiction, Bupropion, Cognitive Behavioural Therapy, Neuromodulation, Tobacco Dependence

I. INTRODUCTION

1.1 Background

Tobacco use remains one of the most significant public health challenges worldwide, with over 1.1 billion people currently using tobacco products and annual deaths exceeding 8 million, including more than 1 million from second-hand smoke exposure [1]. While smoking prevalence has declined in many high-income countries due to effective tobacco control policies, rates remain high or are even increasing in low- and middle-income countries, where over 80% of smokers now reside [2]. This shift has resulted in a growing burden of tobacco-related disease and death in these regions.

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Global Prevalence and Trends

In 2020, global adult smoking prevalence was 32.6% among men and 6.5% among women, with 1.18 billion people regularly smoking tobacco [3].

Although prevalence rates have declined by over 25% since 1990, population growth has led to a stable or increasing absolute number of smokers globally [4].

Most tobacco users and tobacco-related deaths are now concentrated in low- and middle-income countries [5].

Health Impact

Tobacco use is the leading preventable cause of death worldwide, responsible for 7–8.7 million deaths annually and over 200 million disability-adjusted life years (DALYs) lost each year [6].

Smoking is causally linked to at least 36 major health outcomes, including cancers (notably lung, oral, and oesophageal), cardiovascular diseases, chronic respiratory diseases, and stroke [7].

Second-hand smoke exposure causes significant morbidity and mortality, particularly among children and non-smokers [8].

The economic burden of tobacco use is substantial, accounting for nearly 2% of global GDP due to healthcare costs and lost productivity [9].

Regional Disparities and Future Outlook

High-income countries have seen the largest declines in smoking prevalence, while many low- and middle-income countries have experienced slower progress or even increases in tobacco use [10].

Without intensified tobacco control efforts, the global burden of tobacco-related disease and death is projected to remain high or increase, especially in developing regions [11].

Effective smoking cessation strategies are crucial for reducing tobacco-related disease and death

Effective smoking cessation strategies are essential because quitting smoking significantly lowers the risk of cancers, cardiovascular disease, respiratory illness, and premature death, while also improving quality of life and mental health [12].

Health and Societal Impact

Quitting smoking at any age leads to immediate and long-term health benefits, including reduced risk of cancer, heart disease, and respiratory conditions, and improved quality of life [13].

Successful cessation also reduces healthcare costs and the burden on health systems, making it a cost-effective public health intervention [14].

Mental health outcomes improve with successful quitting, with reductions in depression and anxiety symptoms compared to those who continue smoking [15].

Efficacy of Smoking Cessation Strategies

Combined behavioral and pharmacological interventions (e.g., counseling plus nicotine replacement therapy or medications) are the most effective for achieving long-term abstinence [16].

Digital and technology-based interventions, such as mobile apps and automated digital programs, show promise in increasing quit rates and expanding access, especially when grounded in psychological theory [17].

Tailored interventions for specific populations (e.g., those with chronic diseases, older adults, or low socioeconomic status) further enhance effectiveness and address health disparities [18].

1.2 Limitations of Nicotine-Based Therapies

Nicotine Replacement Therapies (NRTs): Common Forms and Key Limitations

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Nicotine replacement therapies—including patches, gums, lozenges, inhalers, and nasal sprays—are widely used to help people quit smoking. While NRTs increase quit rates by 50–70% compared to placebo, they have important limitations that affect their overall effectiveness and user experience [19].

Common Forms of NRT

Patches: Deliver nicotine slowly through the skin over 16–24 hours.

Gums and Lozenges: Provide faster, oral absorption for craving relief.

Inhalers and Nasal Sprays: Offer rapid, short-term nicotine delivery, mimicking some behavioral aspects of smoking [20].

Limitation	Description & Evidence
Slower Nicotine Delivery	NRTs deliver nicotine more slowly and at lower peak levels than cigarettes, which may not fully satisfy cravings, especially for highly dependent smokers.
Incomplete Withdrawal Relief	NRTs reduce but do not eliminate withdrawal symptoms; some users continue to experience cravings and relapse.
Adherence Issues	Many users have difficulty adhering to NRT regimens, especially with gum or lozenges, due to taste, oral irritation, or inconvenience.
Side Effects	Minor side effects are common: skin irritation (patches), mouth/throat irritation (gum, lozenges), and nasal/throat irritation (sprays.

Table 1: *Limitation of NRT.*

1.3 Rationale for Exploring Non-Nicotinic Therapies

There is a growing focus on non-nicotinic therapies for smoking cessation due to the limitations of nicotine-based treatments and the complex, multifaceted nature of tobacco addiction. Non-nicotinic approaches include both alternative pharmacological agents (not based on nicotine) and non-pharmacological interventions (behavioural, psychological, and technological).

Growing Interest in Alternative Interventions

Research Expansion: Recent systematic reviews and meta-analyses highlight a surge in studies on non-nicotinic interventions, including behavioural, psychological, and non-nicotine e-cigarette approaches [25].

Personalization and Combination: Combining non-nicotinic therapies with pharmacological options or tailoring interventions to individual needs may further improve cessation outcomes [26].

1.4 Objectives of the Review

Non-nicotinic therapies encompass a diverse range of pharmacological and non-pharmacological interventions:

Pharmacological Approaches: Recent research highlights several non-nicotinic pharmacotherapies, including nicotine vaccines, anti-nicotine antibodies, nicotine-degrading enzymes, cannabinoid receptor modulators, and repurposed drugs like metformin. These strategies target nicotine's effects peripherally or modulate reward pathways, with promising preclinical results, but most remain in early development and lack robust clinical evidence [27].

Non-Pharmacological Interventions: Systematic reviews and meta-analyses identify cognitive behavioural education, professional counselling, e-health interventions, school-based programs, and non-nicotine e-cigarettes as effective or promising. Behavioural and technology-supported interventions often show similar or higher adherence and effectiveness compared to pharmacological options, though results can vary by population and intervention type [28].

Emerging Modalities: Non-invasive brain stimulation (e.g., rTMS, tDCS) has shown potential in reducing smoking frequency and increasing abstinence, but evidence is limited by small sample sizes and methodological heterogeneity [29].

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Identifying Research Gaps and Future Directions

Despite progress, several gaps persist:

Translational Gaps: Many promising pharmacological strategies (e.g., vaccines, enzymes, cannabinoid modulators) are supported mainly by animal or preclinical studies, with limited human trials [27].

Population Diversity: Most preclinical and clinical studies focus on adult males, with insufficient research on females, adolescents, and individuals with comorbidities or poly-substance use [30].

Methodological Quality: Systematic reviews highlight inconsistent evidence quality, small sample sizes, short follow-up periods, and high risk of bias in many studies, especially for non-pharmacological interventions [31].

Long-Term Outcomes: There is a need for high-quality, large-scale randomized controlled trials assessing long-term effectiveness, safety, and adherence of non-nicotinic therapies [32].

Integration and Personalization: Future research should explore combining non-nicotinic and pharmacological approaches, tailoring interventions to individual needs, and leveraging digital health tools for broader reach and sustained impact [33].

II. CONCEPTUAL FRAMEWORK

2.1 Neurobiology of Nicotine Addiction

Nicotine addiction is primarily driven by its effects on the brain's dopaminergic reward system, particularly the mesolimbic pathway. This system underlies the reinforcing properties of nicotine, making tobacco use highly addictive and difficult to quit.

Core Dopaminergic Circuitry

Mesolimbic Pathway: Nicotine activates dopaminergic neurons in the ventral tegmental area (VTA), leading to increased dopamine release in the nucleus accumbens (NAc). This dopamine surge is central to the rewarding and reinforcing effects of nicotine, promoting repeated use [34].

Nicotinic Acetylcholine Receptors (nAChRs)

Nicotine binds to nAChRs on VTA dopamine neurons, enhancing their firing and dopamine release. Subtypes containing α4, α6, and β2 subunits are especially important for this process [35].

Reinforcement and Learning Mechanisms

Reward and Reinforcement: Dopamine release in the NAc creates pleasurable sensations and reinforces behaviours associated with nicotine intake. This process is like natural rewards but is more persistent and less subject to habituation, leading to strong associative learning and habit formation [36].

Conditioned Cues: Environmental cues paired with nicotine use become conditioned reinforcers, further driving compulsive tobacco-seeking behaviour even in the absence of nicotine [37].

Modulation and Adaptation

Neuroadaptations: Chronic nicotine exposure leads to changes in nAChR expression and dopamine system sensitivity, contributing to tolerance, withdrawal, and persistent craving [38].

Genetic Factors: Variations in genes related to dopamine synthesis, receptors, and metabolism can influence individual susceptibility to nicotine dependence [39].

2.2 Targets Beyond Nicotinic Receptors

Nicotine addiction involves not only nicotinic acetylcholine receptors but also complex interactions with serotonergic, dopaminergic, and glutamatergic systems, each playing distinct roles in reinforcement, craving, and withdrawal.

Dopaminergic System

Central Role in Reward: Nicotine stimulates dopamine release in the mesolimbic pathway (ventral tegmental area to nucleus accumbens), driving reinforcement and compulsive use [40].

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Therapeutic Target: Blocking dopamine D1 receptors reduces nicotine self-administration in animal models, highlighting dopaminergic signalling as a key target for intervention [41].

Serotonergic System

Modulation of Reinforcement: Serotonin (5-HT), especially via 5-HT2C receptors, modulates dopamine release and can inhibit nicotine's rewarding effects [42].

Pharmacological Evidence: Agonists at 5-HT2C receptors (e.g., lorcaserin) and SSRIs (e.g., fluoxetine) reduce nicotine self-administration and conditioned place preference, suggesting serotonergic agents may aid cessation [43].

Genetic Links: Polymorphisms in serotonergic genes (e.g., HTR2A) are associated with nicotine dependence and smoking quantity [44].

Glutamatergic System

Facilitation of Addiction: Nicotine increases glutamate release, which enhances dopamine signalling and reinforces addiction [45].

Therapeutic Potential: Blocking glutamate receptors (NMDA, AMPA, mGluR5) or modulating glutamatergic transmission reduces nicotine-induced dopamine release and self-administration, making this system a promising target for novel therapies [46].

2.3 Defining "Non-Nicotinic Therapies"

Non-nicotinic therapies for smoking cessation are interventions that do not act directly on nicotinic acetylcholine receptors. These approaches can be broadly categorized into pharmacological (non-nicotinic drugs) and non-pharmacological (behavioural and neuromodulatory) interventions.

Pharmacological (Non-Nicotinic Receptor Drugs)

Mechanisms: These drugs target pathways other than nicotinic receptors, such as dopaminergic, serotonergic, glutamatergic, or peripheral nicotine metabolism.

Examples:

Bupropion: Inhibits dopamine and norepinephrine transporters, reducing withdrawal and cravings [47].

Nortriptyline and Clonidine: Affect noradrenergic and adrenergic systems, used as second-line agents due to side effects [48].

Cytisine: A partial agonist at nicotinic receptors, but with a distinct profile from nicotine [49].

Behavioural and Neuromodulatory Interventions

Behavioural Interventions: Include cognitive behavioural therapy (CBT), mindfulness-based interventions, motivational interviewing, counselling, and digital health programs. These target psychological, social, and habitual aspects of addiction [51].

Neuromodulatory Interventions: Techniques like repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) aim to alter brain circuits involved in craving and reward, offering a non-drug approach to reduce smoking [52].

Effectiveness: Behavioural interventions are effective alone or in combination with pharmacotherapy, especially for individuals with mental health comorbidities or high relapse risk [53].

III. PHARMACOLOGICAL NON-NICOTINIC THERAPIES

3.1 Bupropion

Mechanism: Bupropion is a norepinephrine and dopamine reuptake inhibitor, enhancing neurotransmitter levels in reward pathways and reducing withdrawal and craving. It may also have some antagonistic action at nicotinic receptors [54].

Efficacy: High-certainty evidence shows bupropion increases long-term quit rates compared to placebo (RR ~1.6–1.7) [55]. It is as effective as single-form NRT and nortriptyline, but less effective than varenicline or combination NRT [56].

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Safety: Bupropion increases the risk of adverse events (notably insomnia and dry mouth) and trial dropouts, but serious adverse events (including seizures) are rare (about 1 in 1000) [56]. No significant increase in neuropsychiatric events was found, even in those with psychiatric disorders [57].

3.2 Varenicline

Mechanism: Varenicline is a partial agonist at α4β2 nicotinic receptors, directly targeting nicotine's primary site of action.

Efficacy: Varenicline is more effective than bupropion or NRT monotherapy (OR ~1.6–1.8 vs. bupropion) and is often ranked as the most effective single agent [58].

Safety: No significant increase in serious neuropsychiatric or cardiovascular events compared to placebo or bupropion [59].

3.3 Nortriptyline and Other Antidepressants

Mechanism: Nortriptyline is a tricyclic antidepressant, primarily inhibiting norepinephrine reuptake with some dopaminergic effects [60].

Efficacy: Nortriptyline doubles quit rates versus place (RR ~2.0), like bupropion and NRT [61]. SSRIs and MAOIs do not show benefit [61].

Safety: Side effects (dry mouth, sedation) are common but serious events are rare; recommended as a second-line agent [60].

IV. LIMITATIONS OF CURRENT RESEARCH

Research on smoking cessation interventions faces several persistent limitations, including methodological variability, short study durations, and underrepresentation of diverse populations. These issues impact the reliability, generalizability, and equity of findings.

Methodological Variability Across Studies

Intervention and Comparator Differences: There is substantial variability in the content and intensity of both experimental and comparator interventions, including the number of behaviors change techniques and use of pharmacotherapy. This makes it difficult to compare results across studies and can obscure true intervention effects [63].

Reporting Quality: Many studies underreport the active components of interventions, further complicating interpretation and synthesis of evidence [64].

Recruitment and Retention: Recruitment and retention rates vary widely, influenced by recruitment strategies, participant characteristics, and intervention type. Direct, person-to-person recruitment and financial incentives improve retention, while indirect methods and longer follow-up reduce it [65].

Short Duration and Lack of Long-Term Follow-Up

Limited Long-Term Data: Most trials have short follow-up periods, often less than 12 months, which may overestimate intervention effectiveness due to relapses not being captured in the short term [66].

Reduced Effect Over Time: The effectiveness of interventions, especially among disadvantaged groups, tends to diminish at longer follow-up, highlighting the need for studies with extended monitoring [67].

V. FUTURE DIRECTIONS

Advances in smoking cessation are moving toward personalized medicine, integration of digital therapeutics with pharmacotherapy, development of novel non-nicotinic drug targets, and systemic changes in healthcare and policy to improve quit rates and equity.

Personalized Medicine: Genetic and Neurobiological Profiling

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Genetic Markers: Variants in genes such as CHRNA5 and CYP2A6 influence nicotine dependence, cessation success, and response to pharmacotherapy. Tools like the nicotine metabolism ratio (NMR) and polygenic risk scores can help tailor treatments, maximize efficacy and minimize side effects [70].

Clinical Implementation: Early trials show that genetically informed feedback and risk tools are acceptable to patients and can reduce smoking, but more research is needed for widespread adoption [71].

Integration of Digital Therapeutics with Pharmacotherapy

Digital Tools: Digital therapeutics (DTx), including smartphone apps and virtual reality, are increasingly used to support behaviour change, monitor progress, and deliver tailored interventions alongside medications [72].

Effectiveness: DTx can enhance standard treatments, improve adherence, and provide personalized support, but require further study to optimize usability and integration into diverse healthcare systems [73].

Development of Novel Non-Nicotinic Drug Targets

Emerging Pharmacotherapies: New approaches include nicotine vaccines, anti-nicotine antibodies, nicotine-degrading enzymes, cannabinoid receptor modulators, and metformin. These target peripheral nicotine metabolism or alternative neurobiological pathways, showing promise in preclinical and early clinical studies [74].

Glutamatergic Targets: Antagonists of metabotropic glutamate receptor 5 (mGluR5) are under investigation, with preclinical evidence supporting their potential, though withdrawal symptoms and off-target effects remain challenges [75].

Policy and Healthcare System Implications

System-Level Change: Expanding treatment coverage, integrating cessation into routine care, and leveraging digital and stepped-care approaches can substantially increase quit rates at the population level [76].

Equity and Access: Policies must address disparities by ensuring interventions are accessible and tailored to diverse populations, and by supporting clinician training and system-wide adoption.

VI. CONCLUSION

By addressing the intricate neurobiological and behavioural factors underlying nicotine addiction, non-nicotinic-based treatments mark a significant breakthrough in the area of smoking cessation. According to available data, behavioural and technology-based therapies combined with pharmaceuticals like nortriptyline, varenicline, and bupropion can greatly enhance smoking cessation results and lower relapse rates. Novel treatments that target the dopaminergic, serotonergic, glutamatergic, and cannabinoid pathways show a chance for more efficient and individualized treatment plans. Despite encouraging results, the broad use of these treatments is still hampered by issues such a lack of demographic diversity, inconsistent methodology, and inadequate long-term clinical evidence. To increase accessibility, adherence, and long-term abstinence, future research should concentrate on large-scale randomized clinical trials, customized medicine strategies, and the combination of digital medicines with pharmaceutical treatments. All things considered, non-nicotinic therapies present a useful substitute for traditional nicotine-based therapies and have great potential to lessen the financial and health costs regarding tobacco addiction worldwide.

Ethics:

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflict of interest:

The author declares that there is no conflict of interest.

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