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EFFECTIVE ANTI-NARCOTIC AGENTS FOR SMOKING CESSATION: SYSTEMATIC REVIEW

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Abstract

Nicotine is the primary addictive substance in tobacco, driving smoking behavior through rapid delivery to the brain. While nicotine causes addiction, other harmful components in tobacco lead to serious health issues. Understanding nicotine's pharmacology and delivery methods is key to developing effective cessation strategies. The objective is to review the pharmacological mechanisms of nicotine addiction and evaluate the effectiveness of smoking cessation interventions, including nicotine replacement therapy (NRT), electronic cigarettes (e-cigarettes), and pharmacotherapies like varenicline and bupropion SR, with a focus on personalized treatment approaches. A systematic literature review (2019–2024) was conducted using PubMed and Google Scholar. Keywords and truncation strategies identified relevant studies. Out of 100 screened articles, 48 high-quality studies were selected based on journal quality, statistical methods, and clinical relevance. The PRISMA flow diagram guided data selection and synthesis. Strong evidence supports the effectiveness of NRT (patches, gums, sprays, inhalers) and pharmacotherapies (varenicline, bupropion SR, cytisine) in reducing nicotine dependence. Short-acting NRTs help reduce cravings, while patches provide steady nicotine levels. E-cigarettes show promise but vary in safety. Combined treatments and personalized approaches were more effective, especially for high-risk groups like those with psychiatric conditions. It has been concluded that nicotine addiction requires a combination of pharmacological and behavioral interventions. Tailored strategies, guided by pharmacokinetics and patient preferences, are essential to improve quit rates and long-term abstinence.

Keywords: Bupropion SR, Cytisine, E-cigarettes, Tailored strategies, Varenicline

INTRODUCTION

Nicotine, the main addictive substance in tobacco, alters brain chemistry and reinforces smoking habits through rapid delivery to the brain (within 10–20 seconds) (1, 2). While nicotine drives addiction, other tobacco components cause severe health problems, including cancer and respiratory diseases (3). Tobacco smoking is highly addictive due to nicotine's rapid brain effects, while harm comes from other cigarette components. Advances in neurochemistry are aiding pharmacological treatments for cessation.

NRT and cytisine are non-prescription aids for smoking cessation. NRT eases withdrawal by supplying nicotine in forms like patches and gum, while (cytisine, a plant-based nicotine partial agonist), works similarly to varenicline (4). Nicotine replacement therapies (NRTs) help smokers quit by providing nicotine without tobacco, though they work differently than smoking (5, 6). The effectiveness of NRT in aiding smoking cessation is well established, and many clinical guidelines recommend NRT as a first-line treatment for those seeking pharmacological assistance to stop smoking (7). Most NRT forms deliver nicotine more gradually than smoking, leading to a slower increase in nicotine blood levels (8). Nicotine gum (available in 2mg and more effective 4mg doses) raises nicotine levels gradually over 20-30 minutes, with quick-release versions reducing cravings faster (9-11). The effects of nicotine vary between individuals because the brain's nicotinic receptors respond differently based on factors like age, genetics, and how much nicotine gum is used daily. Quick-release nicotine gum works faster than regular gum due to its special formulation that releases nicotine rapidly at first (biphasic delivery) and increases pH for better absorption through the mouth lining. Studies show this quick-release gum reduces cravings more effectively because it delivers nicotine faster to help smokers manage withdrawal symptoms (12). Nicotine sprays deliver nicotine rapidly through the mouth lining but may irritate the throat, while patches provide steady nicotine through



the skin (transdermal delivery) though they may cause skin irritation(13, 14). Nicotine patches provide steady transdermal nicotine delivery in 16-hour (5, 10, 15 mg) and 24-hour (7, 14, 21 mg) doses, raising plasma levels more consistently than short-acting NRTs. Side effects may include skin irritation and insomnia (15, 16). Electronic cigarettes, often known as electronic nicotine delivery systems or e-cigarettes, are battery-powered devices designed to provide nicotine in vapor form to consumers in place of smoke, along with flavorings and other substances. They can resemble conventional tobacco cigarettes, pipes, cigars, or even commonplace items like USB memory sticks or pens (17). While e-cigarettes deliver nicotine quickly like cigarettes, they aren't officially approved for cessation. (18-20). Other medications include bupropion SR, an antidepressant that blocks nicotine effects, and varenicline, a (partial agonist) (drug that partly activates brain receptors) that reduces cravings. These treatments work differently for each person due to factors like genetics and age, and combining methods (like patches with gum) often works best (21-23).

SMOKING HABITS AND CESSATION STRATEGIES IN PAKISTAN

In Pakistan, about 19% of adults use tobacco, with higher rates among men (29%) than women (6%). Common quitting aids include nicotine gum and patches, though access is limited. Public health efforts face challenges including weak policy enforcement and tobacco industry influence. Pakistan needs stronger policies, better access to quitting aids, and public education to reduce smoking (24-27).

OBJECTIVE

The text reviews nicotine addiction's pharmacological basis and cessation strategies, emphasizing nicotine's rapid brain effects and addictiveness. It covers NRT, e-cigarettes, and medications like varenicline and bupropion SR, along with treatment efficacy, absorption, gender differences, and personalized approaches.

METHODOLOGY

LITERATURE SEARCHES

A systematic review (2019–2024) identified 48 high-quality studies on anti-narcotic drugs for smoking cessation using PubMed and Google Scholar. Data were analyzed using PRISMA, though study design and analysis methods varied widely across the literature.

INCLUSION CRITERIA

Articles focusing on the studies on pharmacological agents for smoking cessation. Research on efficacy, safety, and mechanisms of anti-narcotic drugs. Clinical/preclinical evaluations of therapies like varenicline, bupropion, or nicotine replacement. Articles addressing outcomes and side effects of smoking cessation treatments.

EXCLUSION CRITERIA

Articles not directly related to anti narcotic agents for smoking cessation. Studies lacking sufficient detail on methodology or results. Non- peer-reviewed sources, conference abstracts, and editorials.

QUALITY ASSESSMENT

Evaluation of the methodological rigor and quality of included studies using established criteria, such as the PRISMA guidelines for systematic reviews and meta-analyses. Assessment of potential biases, limitations, and confounding factors in individual studies. Consideration of the overall strength of evidence and implications for clinical practice and future research.

IDENTIFICATION OF STUDIES VIA DATABASES

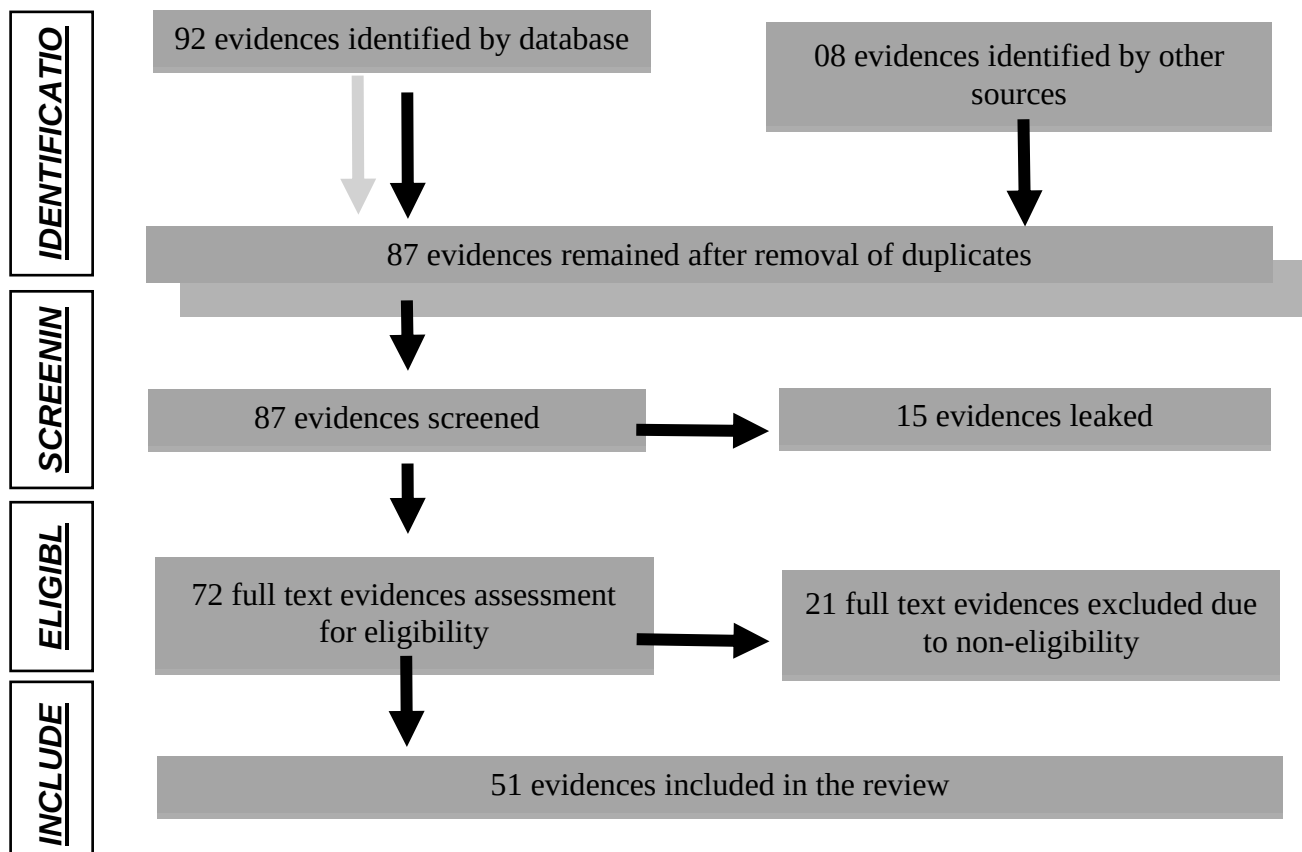


Fig. 1. PRISMA Flow Diagram

RESULTS

Key findings from selected studies are summarized in Table I. These findings emphasize the value of personalized cessation strategies.

Table I. Effective Anti-Narcotic Agents for Smoking Cessation and its outcomes

Title	First author	Year	Study design	Aim & objectives	Result
Comparative effectiveness of group-delivered acceptance and commitment therapy versus cognitive behavioral therapy for smoking cessation: a randomized controlled trial (24)	McClure, Jennifer B	2020	Randomized controlled trial	The study aimed to evaluate the efficacy of group-administered ACT versus group-administered CBT in a strict randomized trial with long-term follow-up.	At the 12-month follow-up, 30-day point prevalence abstinence rates were similar between ACT (13.8%) and CBT (18.1%), with no significant difference (adjusted odds ratio = 0.68, $p = 0.23$). Results were consistent in sensitivity analyses.
QuitNic: a pilot randomized controlled trial comparing nicotine vaping products with nicotine	Bonevski, Billie	2021	The QuitNic pilot randomized controlled trial	Treatment adherence, acceptability, self-reported abstinence, cigarettes smoked per day, craving	Retention rates were 63% at 6 weeks and 50% at 12 weeks. At 12 weeks, 68% of the NRT group used combination NRT,

replacement therapy for smoking cessation following residential detoxification (25)				frequency, and withdrawal symptom severity were assessed at 6 and 12 weeks.	while 96% of the NVP group used the device.
The Effectiveness of E-Cigarettes for Smoking Cessation: A Comparison With Nicotine Replacement Therapy and No Use of Evidence-Based Cessation Aids in the German Population (26)	Kotz, Daniel	2022	cross-sectional study	The primary aim was to assess the effectiveness of e-cigarettes (with or without nicotine), nicotine replacement therapy (NRT), and no evidence-based aids in smoking cessation in the German population.	After adjusting for confounders, smokers who used e-cigarettes (ECs) in their quit attempt had 1.78 times higher odds of abstinence compared to those who used no aids.
E-cigarettes and nicotine abstinence: a meta-analysis of randomized controlled trials (27)	Hanewinkel, Reiner	2022	randomized controlled trials	To determine the effects of electronic cigarettes (e-cigarettes) as a therapeutic intervention compared to nicotine replacement therapy (NRT) on nicotine abstinence.	Compared to NRT, e-cigarette use was associated with lower nicotine abstinence rates at the longest follow-up
Comparative effectiveness of varenicline and nicotine replacement therapy for smoking cessation in older and younger smokers: a prospective cohort in Taiwan (28)	Chang, Po-Yin	2019	A Prospective Cohort study	This study compared the effectiveness of varenicline versus NRT in smokers aged 25–54 and those aged 55 or older.	Among smokers in smokers aged 55 or older, 7-day point-prevalence was similar for varenicline and NRT, with no evidence of greater effectiveness for varenicline. Sex and nicotine dependence did not affect age-specific outcomes.
Effects of combined varenicline with nicotine patch and of extended treatment duration on smoking cessation: a randomized clinical trial (29)	Baker, Timothy B	2021	Double-blind, 2 × 2 factorial randomized clinical trial	The study compared combinations of varenicline with nicotine or placebo patches for either 12 weeks (standard duration) or 24 weeks (extended	In patients assigned to varenicline combination therapy versus monotherapy, the primary outcome was achieved in 24.3% vs. 24.8%, with no significant

duration).
difference (risk difference = 0.4%, OR = 0.99).
Nausea occurred in 24.0% to 30.9%, and insomnia in 24.4% to 30.5% across the four groups.

Exenatide adjunct to nicotine patch facilitates smoking cessation and may reduce post-cessation weight gain: a pilot randomized controlled trial (30)	Yammine, Luba	2021	pilot randomized controlled trial	The study assessed the effectiveness of extended-release exenatide with NRT for smoking cessation, cravings, withdrawal symptoms, and post-cessation body weight.	Post-cessation body weight was 5.6 pounds lower in the exenatide group than placebo. Adverse events occurred in 9.5% of the exenatide group and 2.3% of the placebo group.
Combined nicotine patch with gum versus nicotine patch alone in smoking cessation in Hong Kong primary care clinics: a randomized controlled trial (31)	Leung, Maria KW	2019	a randomized controlled trial	The aim of this study is to compare the effectiveness of combined NRT with single NRT among HK Chinese.	The combined NRT group had a higher abstinence rate (23.6%) than the single NRT group (17.6%) and was more likely to quit (OR 1.43). No significant difference in side effects was found.
Electronic nicotine-delivery systems for smoking cessation (32)	Auer, Reto	2024	open-label, controlled trial,	Primary outcome was biochemically confirmed 6-month abstinence; secondary outcomes included self-reported nicotine/tobacco abstinence, respiratory symptoms, and adverse events.	Serious adverse events occurred in 4.0% (intervention) vs. 5.0% (control); overall adverse events in 43.7% vs. 36.7%, respectively.
Smoking cessation in elective surgical patients offered free nicotine patches at listing: a pilot study (33)	Webb, AR	2020	This pilot study randomized controlled trial	The primary outcome was smoking abstinence for ≥ 4 weeks, as self-reported by participants on the day of	Offering free nicotine patches increased 24-hour quit attempts (11.6% vs. 3.7%, OR 3.4), but 59% relapsed by 6 months,

surgery, including, where possible, corroboration using exhaled carbon monoxide testing.

indicating limited long-term effectiveness.

Titration of nicotine patch doses up to 84 mg/day before quitting and tapering down after led to evaluated responses and 4-week abstinence outcomes.

During the pre-quit period, smoking metrics declined, with 82% achieving 4-week validated abstinence and no withdrawal symptoms reported.

To evaluate the safety and efficacy of smoking cessation pharmacotherapy among smokers with major depressive disorder major depressive disorder (MDD).

Varenicline plus counseling appears most effective for MDD smokers, offering higher efficacy with similar neuropsychiatric risk.

The study compares the effectiveness of nicotine gum and transdermal nicotine patches for smoking cessation in schizophrenic patients in Chennai.

While the study showed reduced smoking, understanding factors behind successful cessation in schizophrenia and other psychiatric disorders may improve treatment strategies.

This study was designed to assess the efficacy and safety of nicotine mouth spray (NMS) in a naturalistic setting in the United States.

The study shows that nicotine mouth spray (NMS) is an effective and safe smoking cessation method for motivated smokers, even without behavioral support.

This study aimed to compare the

Varenicline plus counseling may be



Bupropion, Nicotine Patch, and Placebo on Treating Smoking Among Persons With Current or Past Major Depressive Disorder: Secondary Analysis of a Double-Blind, Randomized, Placebo-Controlled Trial (38)			Placebo-Controlled Trial	safety and efficacy of leading smoking cessation medications in individuals with current versus past major depressive disorder (MDD).	the most effective treatment for individuals with MDD, providing greater efficacy, similar adverse events, and reduced anxiety and depression during smoking cessation.
E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: the TEC RCT (39)	Hajek, Peter	2019	A randomized controlled trial comparing e-cigarettes and NRT.	The objective was to compare the efficacy of refillable e-cigarettes and nicotine replacement therapy (NRT) with weekly behavioral support.	E-cigarette users reported less coughing and phlegm than NRT users after 1 year, and a cost analysis showed e-cigarettes are more cost-effective due to lower NHS costs and higher quit rates.
Nicotine replacement therapy sampling for smoking cessation within primary care: results from a pragmatic cluster randomized clinical trial (40)	Carpenter, Matthew J	2020	Cluster-randomized clinical trial.	We aimed to compare the effects of NRT sampling plus standard care (SC), relative to SC alone, provided by primary care providers during routine clinic visits.	Providing smokers with a free 2-week starter kit of nicotine replacement therapy increased quit attempts, use of stop smoking medications and smoking abstinence compared with standard care in a primary care setting.
Exploring the quality of smoking cessation in community pharmacies: A simulated patient study (41)	Alzubaidi, H.	2022	A cross-sectional, simulated patient (SP) study	To evaluate the quality of community pharmacist smoking cessation counseling in the UAE.	Pharmacist-led smoking cessation programs in the UAE can expand primary care options and meet demand, with pharmacists benefiting from training in smoking cessation and patient-

E-cigarettes versus nicotine replacement treatment as harm reduction interventions for smokers who find quitting difficult: randomized controlled trial (42)	Myers Smith, Katie	2022	Randomized controlled trial	We aimed to test if e-cigarettes (EC) compared with nicotine replacement treatment (NRT) can help such smokers to reduce smoking.	centered communication. The EC group The study found that electronic cigarettes (EC) led to significantly higher smoking cessation rates and product use compared to nicotine replacement therapy (NRT), with minimal adverse effects.
Randomized trial of low-nicotine cigarettes and transdermal nicotine (43)	Smith, Tracy T	2019	A balanced 2 × 2 factorial <u>randomized clinical trial</u>	The present study tested the impact of smoking cigarettes with very low nicotine content and concurrent use of a <u>transdermal nicotine patch</u> .	Both nicotine patches and very low nicotine cigarettes reduced daily cigarette consumption, but combining the patch with low nicotine cigarettes did not significantly enhance smoking reduction.
Varenicline and Nicotine Replacement Therapy for Smokers Admitted to Hospitals: A Randomized Clinical Trial (44)	Weeks, Gregory R	2024	A double-blind, placebo-controlled randomized clinical trial	To examine whether hospitalized smokers treated with varenicline and NRT lozenges achieve higher prolonged smoking abstinence rates compared with those treated with varenicline alone.	The study found similar abstinence rates between intervention and control groups, with the intervention showing significant improvements in long-term abstinence and 7-day point prevalence, though adverse events were comparable.
Smoking Cessation After Initial Treatment Failure With Varenicline or Nicotine Replacement: A Randomized Clinical Trial (45)	Cinciripini, Paul M	2024	Using a double-blind, placebo-controlled, sequential multiple assignment randomized trial	To determine the best subsequent strategy for non-abstinence following initial treatment with varenicline or combined nicotine replacement therapy (CNRT).	The study found that increasing dosages of varenicline and CNRT led to better smoking cessation outcomes, especially for non-abstainers.

Effect of nicotine 6 mg gum on urges to smoke, a randomized clinical trial (46)	Hansson, Anna	2019	randomized crossover clinical study	This study was performed to compare relief of urges to smoke, up until 5 h following treatment with a new 6 mg nicotine gum versus currently marketed 4 mg nicotine gum.	The 6 mg gum was significantly more effective than the 4 mg gum in reducing smoking cravings, with faster and longer-lasting relief.
Using nicotine gum to assist nondaily smokers in quitting: a randomized clinical trial (47)	Shiffman, Saul	2020	A Randomized Clinical Trial	This study tested the effect of nicotine gum, used to prevent or react to situational temptations, for helping non-daily intermittent smokers (ITS) quit.	Nicotine gum showed minimal improvement in smoking cessation, with low usage and no significant differences in abstinence rates compared to placebo.
Smoking Cessation After Initial Treatment Failure with Varenicline or Nicotine Replacement: A Randomized Clinical Trial (48)	Cinciripini, P. M.	2024	double-blind, placebo-controlled, sequential multiple assignment randomized trial	To determine the best subsequent strategy for non-abstinence following initial treatment with varenicline or combined nicotine replacement therapy (CNRT).	Increasing dosages or switching to varenicline led to higher end-of-treatment abstinence rates, with significant improvements in 6-month continuous abstinence.

DISCUSSION

The usage of nicotine vaping products (NVPs) is a novel quitting strategy that has not yet been extensively evaluated in individuals with substance use disorder (SUD). Often referred to as electronic cigarettes (or e-cigarettes), NVPs may be a more effective way to replace nicotine than traditional nicotine replacement therapy (NRT), offering greater alleviation of withdrawal symptoms and cravings. Compared to other smoking cessation medications, NVPs are more behaviorally comparable to smoking cigarettes and entail inhaling vapor created by heating nicotine liquid. This may make them more appealing and acceptable to smokers who wish to stop (28). For smokers who are unable or unable to employ medically approved methods of quitting tobacco, electronic cigarettes (ECs) may be a helpful substitute. It is noteworthy that ECs are currently the most popular quitting aid in Germany, despite medical associations discouraging their usage. Although there are risks associated with ECs, there is mounting evidence that they are far less dangerous than tobacco use. ECs are tobacco-free devices that usually heat a liquid to create a nicotine aerosol that the user inhales. As a result, they provide an action mechanism akin to that of nicotine replacement therapy (NRT) (29). By heating a mixture of propylene glycol, glycerine, flavorings, and nicotine, electronic cigarettes, or e-cigarettes, produce an aerosol. Electronic cigarettes are widely advertised consumer goods in the US, Europe, and many other nations. As consumer goods, e-cigarettes did not result in a higher rate of adult smoking cessation in observational studies. Despite the fact that neither the European Medicines Agency nor the Federal Drug Administration have yet to approve an e-cigarette as a

smoking cessation drug, e-cigarettes have been marketed as smoking cessation aids (30). At any age, including older smokers with more severe nicotine addiction and generally worse health, quitting smoking significantly lowers the risk of tobacco-related morbidity and mortality. Those who smoke and are 65 years of age or older may live an additional 3.7 years after quitting. According to the US Preventive Services Task Force, varenicline and nicotine replacement therapy (NRT) are useful tools for quitting smoking. Compared to a placebo or non-NRT control group, NRT increases the likelihood that smokers would stop smoking by 53% to 68%. In two head-to-head clinical trials, varenicline shown greater or comparable efficacy in achieving abstinence when compared to NRT (31). In addition to raising the risk of death, wound infection, airway hyperreactivity, and postoperative pulmonary problems, smoking causes a variety of other disorders. After just four weeks, quitting smoking dramatically reduces the risk of respiratory and wound complications, making it a crucial part of surgical prehabilitation. National anesthesia bodies' statements and guidelines consistently advise medical professionals to inform smokers about the advantages of quitting before surgery and to provide support. However, there is a great deal of heterogeneity in how health providers and clinicians deliver pre-operative tobacco interventions (32). About one in every 100 persons will experience schizophrenia (SCH), a prevalent disorder. Compared to the general population (about 25%), patients with SCH have greater rates of nicotine dependence from cigarette smoking (58%–88%). They are also frequently highly dependent smokers who struggle to stop. SCH patients may benefit from a variety of possible therapies to help them reduce or quit smoking. It has been demonstrated that nicotine gum helps with withdrawal and doubles the success rate of quitting smoking. It should be mentioned that considering the poor abstinence rates for nicotine chewing gums alone, transdermal nicotine patches (TNPs) are used to help patients quit smoking cigarettes (33). To allow for faster nicotine absorption than with current oral NRT forms, a nicotine mouth spray (NMS) with 1 mg of nicotine per spray has been created. According to a single-dose pharmacokinetic study, NMS 1 or 2 mg had a considerably higher area under the plasma concentration–time curve during the first 10 minutes and a shorter time to maximum plasma nicotine concentration (10–12.5 minutes post-administration) than either 4 mg nicotine gum or lozenge (34).

CONCLUSION

Nicotine vaping products (NVPs), though not yet well-studied in individuals with substance use disorder (SUD), may aid smoking cessation due to their similarity to smoking and ability to ease cravings and withdrawal. While not officially approved, they are increasingly used and likely less harmful than tobacco. Established methods like varenicline and NRT remain highly effective in reducing smoking-related illness and death. Smoking cessation is especially beneficial for high-dependence groups, such as those with schizophrenia, highlighting the need for tailored cessation strategies. Pakistan's smoking epidemic requires "multisectoral efforts", including "policy enforcement, affordable cessation aids, and public awareness". Integrating "WHO's MPOWER strategies" (e.g., monitoring use, protecting non-smokers) could significantly reduce tobacco harm

RECOMMENDATIONS

- Offer NVPs selectively: Use nicotine vaping products for smokers struggling with traditional methods, recognizing the need for more evidence.
- Prioritize proven therapies: Recommend varenicline and NRT as first-line treatments due to their strong efficacy.
- Target high-risk groups: Provide tailored support for individuals with mental health conditions using gum, patches, or nicotine mouth spray.
- Promote pre-surgical quitting: Urge smokers to quit before surgery, offering structured cessation support.
- Expand access to support: Increase availability of cessation programs and personalized counseling to improve quit success.
- Strengthen Tobacco Control Policies: Enforce "higher taxation" on cigarettes and "ban flavored tobacco" to prevent youth use.



- Improve Access to Cessation Aids: Subsidize “NRT and varenicline” in public hospitals.
- Train “community pharmacists” to provide cessation counseling.

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