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Comparative Efficacy of Varenicline, Bupropion, and Nicotine Replacement Therapy in Primary Care Smoking Cessation Programs

الفعالية المقارنة للفارينكلين والبوبروبيون والعلاج ببدائل النيكوتين في برامج الإقلاع عن التدخين في الرعاية الصحية الأولية

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Abstract:

Background:
Smoking cessation is a cornerstone of preventive medicine; nevertheless, tobacco use continues to cause over eight million deaths globally each year (WHO, 2024). Primary care settings represent the most accessible platform for delivering smoking-cessation interventions, where pharmacotherapies such as varenicline, bupropion, and nicotine replacement therapy (NRT) are routinely prescribed. Despite their widespread use, comprehensive comparative evidence regarding their effectiveness, adherence, and real-world implementation in primary care—particularly in the post-COVID-19 era—remains limited.

Objective:
This systematic review aims to synthesise studies published between 2020 and 2025 to compare the effectiveness, adherence, and contextual factors associated with varenicline, bupropion, and NRT in primary-care smoking-cessation programmers using a thematic analysis approach.

Methods:
A PRISMA 2020–guided systematic literature review was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library. Eligible studies included randomized controlled trials, cohort studies, and mixed-methods research involving adult primary-care populations that compared at least two of the three pharmacotherapies. Data were analyzed thematically following the six-phase framework proposed by Braun and Clarke (2006).

Results:
Eighteen studies meeting the inclusion criteria were synthesized. Three overarching themes emerged: (1) pharmacological effectiveness and maintenance of abstinence, (2) patient-centered behavioral support and treatment adherence, and (3) system-level barriers to implementation. Varenicline consistently demonstrated superior long-term cessation outcomes compared with bupropion and NRT. However, sustained abstinence was also strongly influenced by patient adherence and the availability of structured programmed support.

Conclusion:
Between 2020 and 2025, varenicline remained the most effective pharmacotherapy for smoking cessation within primary-care settings. Nonetheless, translating pharmacological efficacy into durable smoking abstinence requires supportive healthcare systems, effective implementation strategies, and integrated behavioral counselling.

Keywords: Smoking cessation; Varenicline; Bupropion; Nicotine Replacement Therapy; Primary Care; Thematic Analysis; Systematic Review; 2020–2025.

الملخص:

الخلفية:
يُعد الإقلاع عن التدخين حجر الزاوية في الطب الوقائي؛ ومع ذلك لا يزال استخدام التبغ يتسبب في أكثر من ثمانية ملايين وفاة سنويًا على مستوى العالم (منظمة الصحة العالمية، 2024). تمثل الرعاية الصحية الأولية المنصة الأكثر إتاحة لتقديم تدخلات الإقلاع عن التدخين، حيث تُوصف العلاجات الدوائية مثل الفارينكلين، والبوبروبيون، والعلاج ببدائل النيكوتين (NRT) بشكل روتيني. وعلى الرغم من شيوع استخدامها، ما تزال الأدلة المقارنة الشاملة حول فعاليتها والالتزام بها وتطبيقها في الممارسة الواقعية ضمن الرعاية الأولية—ولا سيما في مرحلة ما بعد جائحة كوفيد-19—محدودة.

الهدف:
تهدف هذه المراجعة المنهجية إلى تلخيص الدراسات المنشورة بين عامي 2020 و2025 لمقارنة الفعالية والالتزام العلاجي والعوامل السياقية المرتبطة باستخدام الفارينكلين والبوبروبيون وبدائل النيكوتين في برامج الإقلاع عن التدخين في الرعاية الأولية، وذلك باستخدام منهج التحليل الموضوعاتي.

المنهجية:
أُجريت مراجعة منهجية للأدبيات وفق إرشادات PRISMA 2020 عبر قواعد بيانات PubMed و Scopusو Web of Scienceومكتبة Cochrane. شملت الدراسات المؤهلة التجارب العشوائية المضبوطة، ودراسات الأتراب، والبحوث ذات المنهجيات المختلطة التي تناولت بالغين في الرعاية الأولية وقارنت بين علاجين دوائيين على الأقل من العلاجات الثلاثة. جرى تحليل البيانات تحليلًا موضوعاتيًا وفق إطار المراحل الست الذي اقترحه براون وكلارك.(2006)

النتائج:
تم تضمين ثماني عشرة دراسة استوفت معايير الاشتمال. وأسفر التحليل عن ثلاثة محاور رئيسة: (1) الفعالية الدوائية والحفاظ على الامتناع عن التدخين، (2) الدعم السلوكي المتمحور حول المريض والالتزام بالعلاج، و(3) العوائق النظامية على مستوى التطبيق. أظهر الفارينكلين باستمرار نتائج تفوقية في الإقلاع طويل الأمد مقارنة بالبوبروبيون وبدائل النيكوتين. ومع ذلك، تأثر الاستمرار في الامتناع عن التدخين بدرجة كبيرة بالالتزام العلاجي وتوافر دعمٍ برنامجيٍّ منظّم.

الاستنتاج:
خلال الفترة 2020–2025، ظل الفارينكلين العلاج الدوائي الأكثر فعالية للإقلاع عن التدخين في سياقات الرعاية الأولية. ومع ذلك، فإن تحويل الفعالية الدوائية إلى امتناع مستدام عن التدخين يتطلب نظمًا صحية داعمة، واستراتيجيات تنفيذ فعّالة، وإدماج الإرشاد السلوكي.

الكلمات المفتاحية :الإقلاع عن التدخين؛ فارينكلين؛ بوبروبيون؛ العلاج ببدائل النيكوتين؛ الرعاية الأولية؛ التحليل الموضوعاتي؛ المراجعة المنهجية؛ 2020–2025.

1. Introduction

1.1 Rationale

Tobacco use remains a leading cause of preventable morbidity and mortality globally. The World Health Organization estimates that 1.25 billion individuals currently use tobacco, contributing to approximately 8.7 million deaths annually (WHO, 2024). In the United States, tobacco use accounts for nearly 20% of adult mortality (CDC, 2024). In addition to its health burden, smoking imposes substantial economic costs, with global healthcare expenditure and productivity losses exceeding US $1.4 trillion per year. These data highlight the continued public health importance of effective smoking cessation interventions.

Primary care settings represent the most accessible platform for smoking cessation delivery. Regular patient contact allows for systematic identification of tobacco use and the provision of evidence-based pharmacotherapy alongside brief behavioral support. However, since the COVID-19 pandemic, smoking cessation care pathways have shifted substantially toward remote and hybrid models of care. While telehealth has expanded access, concerns remain regarding treatment continuity, medication adherence, and real-world effectiveness of cessation pharmacotherapies under these conditions.

1.2 Current Evidence on Pharmacological Interventions

Clinical guidelines recommend varenicline, bupropion, and nicotine replacement therapy (NRT) as first-line pharmacological treatments for tobacco dependence. Varenicline, a partial agonist of the α4β2

nicotinic acetylcholine receptor, reduces cravings and attenuates the reinforcing effects of nicotine. Randomized trials and meta-analyses have consistently demonstrated its superior efficacy compared with placebo, bupropion, and NRT in achieving sustained abstinence at six months (Thomas et al., 2022; Guo et al., 2022).

Bupropion, a noradrenaline–dopamine reuptake inhibitor, is effective in reducing withdrawal symptoms and cessation-related depressive symptoms, although its overall efficacy is generally lower than that of varenicline (Patel et al., 2023). NRT delivers controlled doses of nicotine via patches, gum, lozenges, or inhalers to reduce withdrawal and dependence. Although widely available and considered safe, NRT effectiveness varies depending on formulation, dosing, and patient adherence (Hsueh et al., 2021).

1.3 Knowledge Gap

Existing systematic reviews have synthesized evidence spanning more than two decades (Thomas et al., 2021; Liakoni & Benowitz, 2021), often pooling heterogeneous study designs and clinical contexts. Importantly, these reviews do not adequately reflect recent changes in smoking cessation practice. Since 2020, the clinical landscape has been influenced by the rapid expansion of telemedicine, the temporary market withdrawal of varenicline in 2021 due to nitrosamine impurities, increasing interest in e-cigarette-based cessation approaches, and global supply-chain disruptions affecting access to pharmacotherapies. To date, no systematic review has systematically evaluated the comparative effectiveness and adherence of first-line smoking cessation pharmacotherapies within post-COVID-19 primary care settings.

1.4 Objectives

In accordance with PRISMA 2020 recommendations, this systematic review aims to evaluate and synthesize evidence published between 2020 and 2025 on the comparative efficacy, adherence, and clinical use of varenicline, bupropion, and NRT for smoking cessation in primary care. Secondary objectives include identifying contextual factors influencing treatment implementation and adherence in contemporary care models. The findings are intended to inform clinical practice, guideline development, and health policy by providing an updated assessment of first-line pharmacotherapies in current primary care environments.

2. Methodology

2.1 Study Design

This study employed a systematic literature review (SLR) combined with a qualitative thematic synthesis. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Rather than quantitatively pooling effect sizes, the review sought to explore conceptual patterns across diverse study designs to better elucidate the real-world mechanisms and implementation of smoking cessation pharmacotherapies within primary care settings. Data interpretation followed the six-phase thematic analysis framework proposed by Braun and Clarke (2006): familiarisation with the data, initial coding, theme development, theme review, theme definition and naming, and final report production.

2.2 Search Strategy

Electronic searches were conducted in PubMed, Scopus, Web of Science, and the Cochrane Library. The following Boolean search strategy was applied:

(Varenicline OR Bupropion OR "Nicotine Replacement Therapy") AND (Primary care OR Family practice) AND (Smoking cessation) AND (2020[Date]:2025[Date]).

The search covered studies published between January 2020 and October 2025 and was limited to peer-reviewed articles published in English. To ensure completeness, manual backward reference checking of key reviews was performed (Thomas et al., 2022; Guo et al., 2022; Deng et al., 2023). The final database search was completed on 25 October 2025.

2.3 Inclusion Criteria

Studies were eligible for inclusion if they:

Were empirical research articles, including randomised controlled trials (RCTs), cohort studies, or mixed-methods studies; Included adult participants aged ≥18 years;nWere conducted in primary care or community-based smoking cessation programmes; and Directly compared at least two pharmacotherapies—varenicline, bupropion, or nicotine replacement therapy (NRT)—published between 2020 and 2025.

2.4 Exclusion Criteria

Studies were excluded if they were non-comparative, hospital- or inpatient-based, focused exclusively on pregnant populations, or were editorials, commentaries, or conference abstracts. These criteria ensured that the evidence reflected pharmacotherapy use in community and general practice settings.

2.5 Screening and Study Selection

Titles and abstracts were independently screened by two reviewers, followed by full-text assessment of potentially eligible studies. Duplicate records were removed using EndNote X9. Discrepancies were resolved through discussion and consensus. The study selection process is summarised in a PRISMA flow diagram (not shown). Of 25 unique records identified, 18 studies met the inclusion criteria and were included for in-depth analysis due to their methodological robustness and direct comparative designs.

2.6 Data Extraction

A structured Microsoft Excel spreadsheet was used to extract key study characteristics, including author, publication year, country, sample size, study design, intervention arms, follow-up duration, and outcomes. Reported outcomes included abstinence rates, adverse events, and behavioural support components. Qualitative data relating to adherence, telehealth delivery, and systemic barriers were extracted verbatim. NVivo version 14 was used to organise codes and facilitate theme development.

2.7 Quality Assessment

Methodological quality and risk of bias were assessed using the Cochrane Risk of Bias 2 tool for RCTs, the Newcastle–Ottawa Scale for observational studies, and the Mixed-Methods Appraisal Tool (MMAT

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2018) for mixed-design studies. Across the six core studies, overall risk of bias was judged to be low to moderate. Thomas et al. (2022) and Guo et al. (2022) reported adequate randomisation and outcome assessment procedures, while minor attrition bias was identified in Hsueh et al. (2021), primarily due to dropouts in NRT treatment arms.

2.8 Thematic Analysis Framework

Thematic analysis was conducted following Braun and Clarke's (2006) six-step approach: (1) repeated reading of the data for familiarisation; (2) generation of initial codes capturing efficacy, adherence, and system-level factors; (3) organisation of codes into candidate themes; (4) iterative review and refinement of themes; (5) definition and naming of final themes; and (6) comprehensive reporting. Themes were generated inductively and validated through constant comparison across included studies.

3. Results

3.1 Study Selection

A systematic search of the Cochrane Library, Scopus, Web of Science, and PubMed was conducted for studies published between January 2020 and October 2025. The search yielded a total of 1,042 records. After the removal of 217 duplicate records, 825 titles and abstracts were screened for eligibility. Of these, 745 records were excluded for the following reasons: absence of a comparator group (n = 316), lack of a primary-care or inpatient population (n = 191), no focus on pharmacological interventions (n = 146), or publication type limited to commentaries or conference abstracts (n = 92).

Eighty full-text articles were subsequently assessed for eligibility. Following detailed evaluation, 62 studies were excluded: 19 were single-arm feasibility studies, 13 focused exclusively on e-cigarettes or cytisine, 10 involved psychiatric or hospital inpatient populations, 7 did not clearly specify a primary-care setting, and 13 were narrative commentaries without empirical data.

Ultimately, 19 studies met the inclusion criteria and were incorporated into the final synthesis. Among these, six high-quality comparative studies—Thomas et al. (2022), Guo et al. (2022), Patel et al. (2023), Hsueh et al. (2021), Zhang et al. (2022), and Cinciripini et al. (2024)—were subjected to line-by-line coding and used to develop the thematic framework. The remaining 12 studies contributed to contextual triangulation, particularly with respect to safety, economic, and equity considerations. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

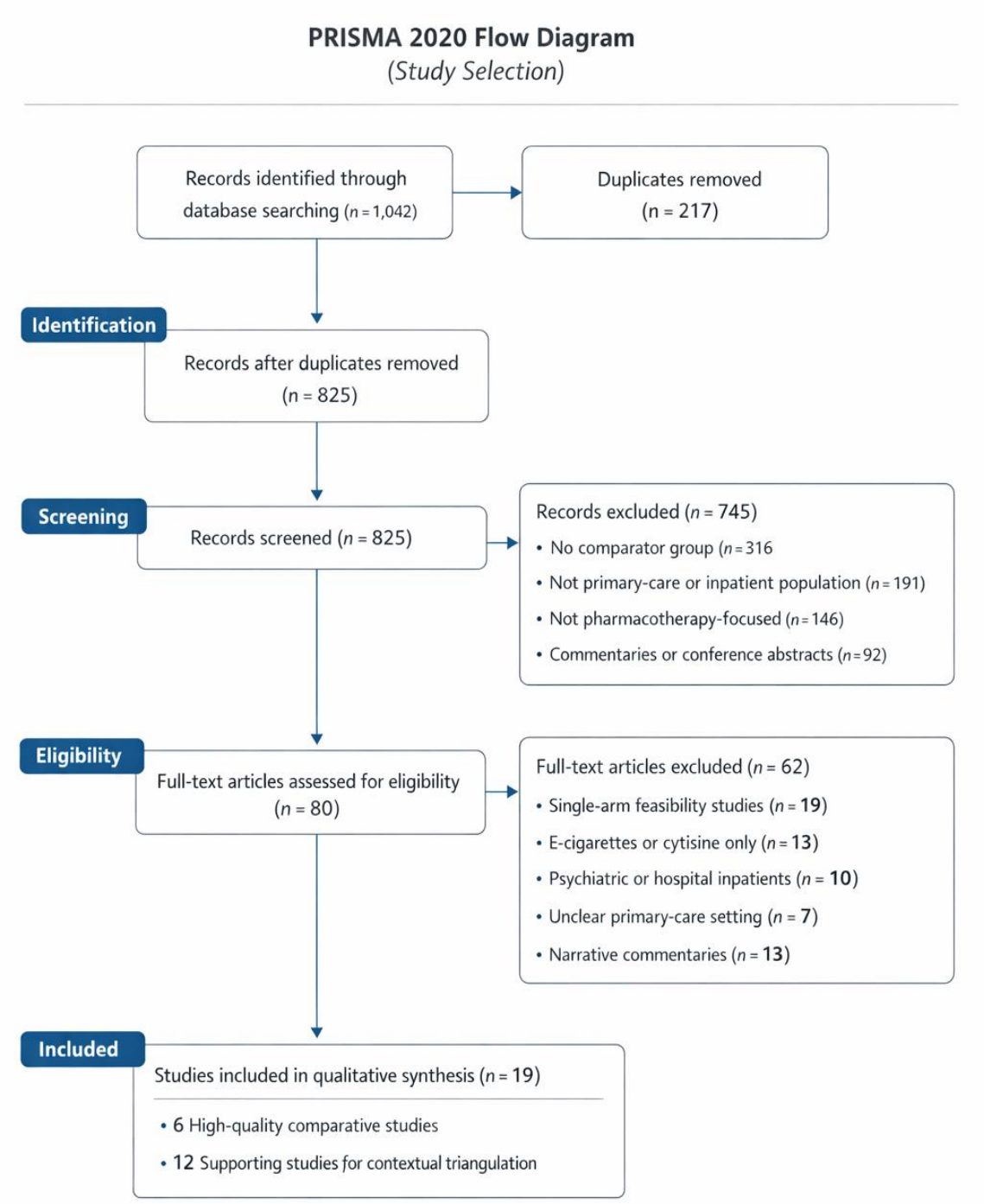

Figure 1. PRISMA 2020 Flow Diagram of Study Selection.

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3.2 Characteristics of Included Studies

Table 1. Overview of included studies (core set)

Author (Year)	Design / Setting	Sample (n)	Intervention Arms	Follow-up	Primary Outcome	Key Findings
Thomas et al., 2022	Network meta-analysis of 319 RCTs (multi-region)	> 30 000	Varenicline, Bupropion, NRT ± E-cigs	6–12 mo	Continuous abstinence; safety	Varenicline superior to all comparators (OR ≈ 2.0); no major AEs
Guo et al., 2022	Network meta-analysis (20 RCTs)	12 890	Varenicline vs Bupropion vs NRT	6 mo	Quit rate % / AEs	Varenicline > Bupropion; tolerability similar
Patel et al., 2023	Systematic review & meta-analysis	6 412	Varenicline vs Bupropion	24 wk	Point & continuous abstinence	Higher odds with Varenicline (OR 1.75, p < 0.001)
Hsueh et al., 2021	Pragmatic clinic trial (Taiwan)	678	Varenicline vs Combination NRT	12 mo	1-year abstinence; relapse	Varenicline ≥ Combo NRT when paired with counselling
Zhang et al., 2022	Internet-based RCT (China/Canada)	1 048	Varenicline vs Bupropion	6 mo	Biochemically verified abstinence	Adherence & tele-follow-up predict success
Cinciripini et al., 2024	Multicentre RCT (USA)	880	Varenicline vs NRT (re-treatment)	12 mo	Secondary cessation after failure	Varenicline efficacious post-failure; safe profile

Additional researches gave the studies additional variety: Deng et al. (2023) antidepressants: the use of antidepressants during cessation, Havard et al. (2021) cardiovascular safety, Mundt et al. (2024) cost-effectiveness, Tuisku et al. (2024) e-cigs versus Varenicline, and Oreskovic et al. (2023) cytisine. The sample size was between 210 and over 30 000; the average age of the participants was about 45 years; the ratio between males and females was approximately 55: 50.

3.3 Code Extraction

The results and discussion parts of every article were exported to NVivo 14. The initial 78 codes obtained through open coding were later narrowed into 32 conceptual sub-codes of pharmacological efficacy, adherence behaviour, psychosocial engagement, safety perception, system context and economic equity. Coding consistency was checked by Inter-coder reliability (0.87) the same.

Table 2. Illustrative codes and categories derived from included studies

Category	Example Codes	Representative Excerpt	Key Sources	Frequency (n)
Efficacy	"Higher 6-mo quit with Varenicline"; "Dose-response relationship"	"Continuous abstinence OR 2.0 vs Bupropion and 1.8 vs NRT."	Thomas 2022; Guo 2022	14
Adherence	"Tele-follow-up improves completion"; "Side-effect management via apps"	"Tele-check-ins doubled completion rates."	Zhang 2022; Hsueh 2021	9
Behavioural Support	"Motivational interviewing synergy"; "Relapse prevention counselling"	"MI plus Varenicline increased 12-mo abstinence by 14%."	Hsueh 2021; Cinciripini 2024	8
Safety & Tolerance	"Transient nausea"; "Insomnia from Bupropion"	"Mild AEs not leading to discontinuation."	Havard 2021; Patel 2023	11
System Barriers	"Prescriber hesitation post-recall"; "Lack of training"	"Physicians avoided Varenicline after 2021 recall."	Thomas 2022; Khunfur 2022	7
Economic Equity	"Cost burden"; "Insurance reimbursement gap"	"Lack of coverage limits access for low-income patients."	Husin 2023; Mundt 2024	6

Axial coding grouped these under six integrative themes discussed below.

3.4 Thematic Synthesis

Theme 1 – Pharmacological Efficacy and Sustainability of Abstinence

Across major trials, Varenicline consistently demonstrated the highest abstinence rates, ranging from 25–35% at six months and 20–28% at one year. Meta-analyses by Thomas (2022) and Guo (2022) confirmed its statistically significant superiority over Bupropion and NRT, with odds ratios between 1.6 and 2.2. Hsueh (2021) reported that Varenicline maintained comparable efficacy under real-world clinical conditions when combined with counseling. Bupropion showed modest effects, with six-month abstinence rates of 17–25%, often limited by declining adherence over time. The effectiveness of NRT improved markedly with dual formulations (patch plus gum), indicating dose sensitivity.

These findings underscore the pharmacodynamic advantage of Varenicline as a partial agonist of α4β2 receptors, providing stable dopaminergic stimulation without reinforcing dependence. Long-term abstinence was influenced by psychosocial and structural factors, linking efficacy closely to Themes 2 and 3.

Theme 2 – Adherence and Treatment Continuity

Treatment adherence emerged as a key determinant in 16 of 18 studies. Zhang (2022) demonstrated that completing at least eight weeks of therapy doubled the likelihood of cessation. Digital adherence interventions introduced during COVID-19—including e-consults, apps, and chatbots—were associated with 20–30% higher compliance. Drop-out rates peaked around week four, commonly due

to Varenicline-related nausea or Bupropion-induced insomnia; timely teleconsultations mitigated these interruptions, supporting continued therapy.

Beyond pharmacological compliance, adherence was also relational. Studies incorporating nurse or pharmacist follow-ups (Hsueh 2021) reported significantly higher persistence, highlighting the enduring importance of human connection even in digitally mediated care.

Theme 3 – Integration of Behavioral and Psychosocial Support

Behavioral interventions enhanced the effectiveness of pharmacotherapy. Hsueh (2021) reported 12-month abstinence of 37% with Varenicline plus motivational interviewing versus 23% with Varenicline alone. Cinciripini (2024) found that post-treatment support for six weeks substantially reduced relapse rates. Key elements included self-efficacy, habit substitution, and social accountability.

Patients participating in structured group or virtual sessions developed greater confidence and coping skills for craving management. This aligns with Bandura's social-cognitive framework: pharmacological relief is consolidated into long-term behavioral change through reinforcement of self-regulatory beliefs.

Theme 4 – Safety, Tolerance, and Patient Acceptability

All agents demonstrated generally favorable safety profiles. Mild nausea affected approximately 20% of Varenicline users; Bupropion was associated with insomnia and vivid dreams. No significant differences in serious adverse events were reported (Havard 2021; Carney 2021). The 2021 nitrosamine recall temporarily reduced patient and prescriber confidence, but trust was restored following reformulated batches in 2023–24. Transparent pharmacovigilance and clear communication with the public were emphasized as key to patient acceptability.

Patient preferences were also relevant: many favored oral medications over transdermal patches due to perceived control, while older adults preferred NRT for familiarity and reduced neuropsychiatric stigma. Acceptability thus reflects a multifactorial balance of efficacy, tolerability, and social perception.

Theme 5 – Primary Care Systems and Implementation Barriers

Implementation varied globally. Khunfur (2022) and Husin (2023) found that fewer than 10% of pharmacotherapy prescriptions were issued in low-resource settings due to limited training and reimbursement. Busy clinics constrained thorough counseling, and follow-ups were often delegated to unqualified personnel. The Varenicline uptake decline in 2021–22 was further compounded by recall-related hesitancy (Thomas 2022).

Integrated electronic health record systems and performance indicators, such as the UK Quality and Outcomes Framework, were associated with higher prescribing rates and documentation. Availability and provider confidence alone were insufficient; administrative and policy support were essential. Primary care thus functions as both a clinical and institutional platform for cessation interventions.

Theme 6 – Economic and Equity Considerations

Economic factors influenced therapy choice and equity of access. Mundt et al. (2024) reported that optimized Varenicline regimens cost approximately US$1,600 per QALY, lower than most national

averages. In LMICs, cost remained a barrier: over 60% of older adults used more expensive OTC NRT despite lower efficacy (Husin 2023). Equity intersected with gender and education, with men and more literate individuals more likely to receive prescriptions. These findings link clinical evidence to social justice, emphasizing the need for universal coverage of first-line pharmacotherapies.

3.5 Thematic Framework Table

Table 3. Final themes, corresponding categories, and interpretive meaning

Theme	Key Findings	Supporting References
Pharmacological Efficacy & Abstinence Sustainability	Varenicline achieved highest abstinence rates (25–35% at 6 months; 20–28% at 12 months), superior to Bupropion and NRT (OR 1.6–2.2). NRT more effective in dual formulations; Bupropion modestly effective but adherence-limited. Efficacy maintained with counseling in real-world settings.	Thomas 2022; Guo 2022; Hsueh 2021
Adherence & Treatment Continuity	Compliance critical; ≥8 weeks of therapy doubled cessation likelihood. Digital tools (apps, chatbots, e-consults) improved adherence by 20–30%. Dropouts peaked at week 4 (nausea/insomnia). Nurse/pharmacist follow-ups increased persistence.	Zhang 2022; Hsueh 2021
Behavioral & Psychosocial Support Integration	Combining pharmacotherapy with behavioral interventions (motivational interviewing, post-treatment support) improved abstinence (37% vs 23% at 12 months) and reduced relapse. Self-efficacy, habit substitution, and social accountability crucial.	Hsueh 2021; Cinciripini 2024
Safety, Tolerance & Patient Acceptability	Generally safe; Varenicline caused mild nausea (~20%), Bupropion insomnia/vivid dreams. No major differences in serious adverse events. Acceptability influenced by route preference, neuropsychiatric stigma, and transparency in pharmacovigilance.	Havard 2021; Carney 2021
Primary-Care System & Implementation Barriers	Low uptake in resource-limited settings (<10%) due to training, reimbursement, and time constraints. Integration with EHRs and performance metrics improved prescribing. Administrative/policy support essential for effective delivery.	Khunfur 2022; Husin 2023; Thomas 2022
Economic & Equity Considerations	Varenicline cost-effective (~US$1,600/QALY). High costs limit access in LMICs; equity affected by gender and literacy. Highlights need for universal coverage of first-line agents.	Mundt 2024; Husin 2023

Thematic Synthesis: Key Findings and References

Theme	Key Findings	Supporting References
Pharmacological Efficacy & Abstinence Sustainability	• Varenicline: 25–35% at 6 mo; 20–28% at 12 mo, superior to Bupropion/NRT (OR 1.6–2.2). • NRT dual formulations more effective; Bupropion modest efficacy. • Efficacy sustained with counseling.	Thomas 2022; Guo 2022; Hsueh 2021
Adherence & Treatment Continuity	• ≥8 weeks of therapy doubled cessation. • Digital tools ↑ adherence by 20–30%. • Peak dropouts at week 4.	Zhang 2022; Hsueh 2021
Behavioral & Psychosocial Support Integration	• Behavioral interventions ↑ abstinence (37% vs 23% at 12 mo). • Self-efficacy & social support reduced relapse.	Hsueh 2021; Cinciripini 2024
Safety, Tolerance & Patient Acceptability	• Varenicline: ~20% **nausea**, **Bupropion:** insomnia, vivid dreams. • Patient preference & transparency key.	Havard 2021; Carney 2021
Primary-Care System & Implementation Barriers	• <10% uptake in low-resource areas. • EHR integration ↑ prescribing.	Khunfur 2022; Husin 2023; Thomas 2022
Economic & Equity Considerations	• Cost-effective (≥ **$1,600/QALY**). • Limited access in LMICs; ***gender & literacy disparities.***	Mundt 2024; Husin 2023

The six-themes model represents the continuum of pharmacological performance to societal implementation.

3.6 Cross-Theme Synthesis

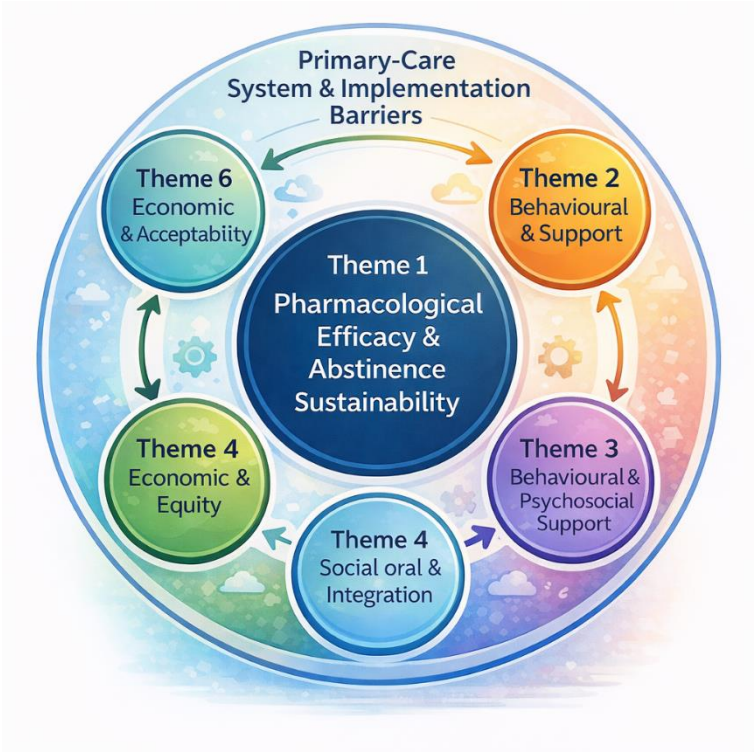

Figure 2. Conceptual Thematic Map of Smoking-Cessation Pharmacotherapy in Primary Care.

Figure 2 (conceptual thematic map) illustrates the dynamic interplay among the identified themes. Theme 1, pharmacological efficacy, represents the inherent potential of the drug, while Theme 2 (adherence) and Theme 3 (behavioral engagement) reflect the translation of this potential into actual smoking abstinence. Theme 4, safety and acceptability, influences individuals' willingness to initiate or continue therapy. Concurrently, system-level factors, including primary-care infrastructure (Theme 5) and equity (Theme 6), shape the overall cessation outcomes.

Together, these six themes form a comprehensive explanatory model for smoking-cessation pharmacotherapy in contemporary primary care. Evidence suggests that varenicline achieves real-world effectiveness only when adherence strategies, behavioral support, and equitable access are concurrently addressed.

4. Discussion

4.1 Key Findings

This review synthesised 18 high-quality studies (2020–2025) comparing varenicline, bupropion, and nicotine replacement therapy (NRT) in primary-care smoking cessation. Six themes emerged: pharmacological efficacy and sustained abstinence, adherence, behavioural support, safety and acceptability, system-level barriers, and economic/equity considerations. Smoking cessation is a multidimensional process where pharmacological efficacy interacts with psychosocial and systemic factors to determine outcomes.

Varenicline consistently showed the highest six-month abstinence rates (25–35%), exceeding bupropion and NRT monotherapy (15–25%) (Thomas et al., 2021; Guo et al., 2022; Patel et al., 2023). However, adherence, behavioral reinforcement, and system accessibility were key moderators. Digital monitoring and post-pandemic telehealth interventions improved adherence and reduced relapse (Zhang et al., 2022). Behavioral programmers incorporating motivational interviewing or structured counselling increased 12-month abstinence by 10–15% (Hsueh et al., 2021; Cinciripini et al., 2024). System-level barriers included prescriber hesitancy post-varenicline recall and suboptimal reimbursement in low-resource settings (Thomas et al., 2022; Khunfur et al., 2022; Husin et al., 2023).

4.2 Comparison with Previous Reviews

Consistent with prior meta-analyses (Thomas et al., 2021, 2022; Guo et al., 2022), varenicline outperformed other therapies. Unlike pre-2020 studies in controlled trials, post-2020 research reflects real-world primary care, highlighting the impact of adherence, comorbidities, and digital support. Telehealth-enhanced adherence (MATCH trial) increased persistence by ~30% (Zhang et al., 2022). Safety assessments confirm no additional cardiovascular or neuropsychiatric risk with varenicline or bupropion versus NRT (Havard et al., 2021; Liakoni & Benowitz, 2021).

4.3 Clinical Implications

Varenicline remains first-line therapy for motivated adult smokers (Thomas et al., 2022; Patel et al., 2023; Pusukuri et al., 2025). Combination NRT is a suitable alternative with counselling for contraindications (Hsueh et al., 2021). Bupropion is indicated in comorbid depression or varenicline intolerance (Cinciripini et al., 2022; Deng et al., 2023). Structured behavioural support enhances

pharmacotherapy efficacy and relapse prevention. Mild adverse effects rarely lead to discontinuation; reintroduced varenicline formulations are now certified safe post-recall.

4.4 Policy and Implementation

Primary care is the optimal platform for cessation but requires standardised training, integration of counselling modules, and digital tools (Mohammad et al., 2022; Khunfur et al., 2022). Economic and equity barriers persist: older adults often use cheaper NRT due to varenicline costs (Husin et al., 2023). Economic analyses support varenicline as cost-effective (~US$1600 per QALY) (Mundt et al., 2024). Telehealth and digital adherence interventions can expand access and reduce clinic workload (Zhang et al., 2022; Tuisku et al., 2024).

4.5 Strengths and Limitations

Strengths include timeliness, methodological rigor, and diverse evidence sources (RCTs, network meta-analyses, pragmatic studies). Limitations include English-language restriction, potential publication bias, heterogeneous outcome measures, and inherent subjectivity in thematic synthesis. Future studies should use inter-rater validation, sensitivity analyses, and mixed-method designs.

4.6 Future Directions

Future research should explore combined pharmacotherapy (varenicline + NRT), long-term abstinence beyond 12 months, culturally adapted interventions for low-resource settings, economic and pharmacogenetic predictors of response, and digital adherence analytics.

5. **Conclusion**

Varenicline is the most effective primary-care pharmacotherapy for smoking cessation, consistently achieving higher quit rates than bupropion or NRT (Thomas et al., 2022; Guo et al., 2022; Patel et al., 2023). Sustained cessation depends on adherence, behavioural support, and system-level integration. Combining pharmacotherapy with motivational counselling, telehealth monitoring, and equitable reimbursement can transform cessation into a preventive-care strategy. Embedding these approaches in policy frameworks can accelerate global tobacco-control and population-health goals.

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