OPEN ACCESS

**Saudi Journal of Medical and Pharmaceutical Sciences**

Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

**Review Article** **Medicine**

# Efficacy and Adverse Effect of Varenicline (Champix) in Cessation of Smoking: Systematic Review

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**DOI:** https://doi.org/10.36348/sjmps.2025.v11i10.007 | **Received:** 24.08.2025 | **Accepted:** 13.10.2025 | **Published:** 15.10.2025

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## Abstract

***Background:*** Varenicline represents the most effective first-line pharmacotherapy for smoking cessation, though post-marketing safety concerns historically limited utilisation. Contemporary evidence requires synthesis following resolution of neuropsychiatric safety signals and emerging applications in diverse populations. ***Objective:*** To evaluate varenicline efficacy and safety for smoking cessation through systematic review of evidence published January 2020-October 2025. ***Methods:*** Comprehensive search across PubMed/MEDLINE, Scopus, Web of Science, and EMBASE identified randomised controlled trials, systematic reviews, and meta-analyses. Two reviewers independently screened records using predefined PICO criteria: adults ≥18 years with current smoking status; varenicline monotherapy at standard dosing; placebo/active comparators; biochemically verified continuous abstinence ≥6 months. Data extraction captured efficacy outcomes, safety profiles, and population-specific effects. Risk of bias assessment employed Cochrane RoB 2 methodology. ***Results:*** Database searching retrieved 3,247 records, with 15 studies meeting inclusion criteria after systematic screening. Studies encompassed 8 randomised controlled trials, 4 systematic reviews/meta-analyses, 2 network meta-analyses, and 1 observational study, representing >15,000 participants across diverse populations. Varenicline demonstrated superior efficacy versus placebo across all populations, with 6-month continuous abstinence rates of 22.1% versus 8.9% (OR 3.14, 95% CI 2.21-4.46, p<0.001). Particularly robust effects were observed in cardiovascular disease patients (OR 4.12, 95% CI 2.89-5.87) and dual cigarette-e-cigarette users (OR 4.95, 95% CI 2.29-10.70). Safety analysis across >8,000 participants showed no significant increase in serious adverse events (6.8% vs 5.9% placebo, OR 1.23, 95% CI 0.95-1.59, p=0.11), including neuropsychiatric (OR 1.25, 95% CI 0.73-2.14, p=0.42) and cardiovascular events (OR 1.35, 95% CI 0.71-2.56, p=0.36). Nausea remained the most common adverse effect (28.6% vs 9.2% placebo) but proved dose-dependent and transient. ***Conclusions:*** Contemporary evidence strongly supports Varenicline as highly effective and acceptably safe first-line therapy for smoking cessation across diverse adult populations, including those with cardiovascular disease and psychiatric disorders. Historical safety concerns have been definitively resolved, supporting broader clinical implementation within established guidelines.

**Key words:** Varenicline; Champix; efficacy and safety; smoking cessation; systematic review.



## BACKGROUND

Varenicline, a selective partial agonist of the α4β2 nicotinic acetylcholine receptor, was first approved by the FDA in 2006 and represents the most recent addition to first-line smoking cessation pharmacotherapy [1-4].

Tobacco smoking remains the leading preventable cause of morbidity and mortality globally, with over 1.1 billion smokers worldwide causing approximately 8 million deaths annually. Despite substantial public health efforts, smoking cessation rates remain disappointingly low, with only 3-5% of unassisted quit attempts achieving 6-month abstinence. Pharmacological interventions, particularly when combined with behavioural support, significantly improve cessation outcomes compared to behavioural interventions alone [5-7].

The drug's unique mechanism involves binding to nicotinic receptors with moderate activation (reducing withdrawal symptoms) while simultaneously blocking nicotine's reinforcing effects, theoretically providing superior efficacy compared to nicotine replacement therapy (NRT) or bupropion. However, post-marketing safety concerns emerged regarding neuropsychiatric adverse events and potential cardiovascular risks, leading to black box warnings that were only removed following comprehensive safety evaluations. [8,9,4,10,11]

Recent developments have renewed interest in varenicline's clinical utility. The landmark EAGLES trial, published in 2016, demonstrated no significant increase in serious neuropsychiatric events compared to placebo across 8,144 participants with and without psychiatric histories. Subsequently, supply chain disruptions in 2021 due to nitrosamine impurities highlighted varenicline's critical role in population-level smoking cessation efforts. Additionally, emerging evidence suggests potential benefits of combination therapy approaches and effectiveness in specialized populations including hospitalized patients and dual users of cigarettes and e-cigarettes. [12-14,9,10,11]

Contemporary smoking cessation guidelines emphasize individualized treatment approaches, with varenicline consistently recommended as first-line therapy. However, questions remain regarding optimal dosing strategies for patients experiencing adverse effects, effectiveness in specific populations, and comparative effectiveness of combination approaches. The evolving tobacco landscape, including increased e-cigarette use and changing smoking patterns during the COVID-19 pandemic, necessitates updated evidence synthesis to inform clinical practice and policy decisions. [15,16,6,17,13]

## OBJECTIVES

The primary objective of this systematic review was to evaluate the efficacy and safety of varenicline monotherapy at standard dosing (0.5 mg once daily days 1-3, 0.5 mg twice daily days 4-7, then 1 mg twice daily for up to 12 weeks) for smoking cessation in adults, compared to placebo, active comparators, or usual care. Secondary objectives included assessing effectiveness across diverse populations (cardiovascular disease, psychiatric disorders, hospitalized patients), evaluating combination therapy approaches, and synthesizing contemporary safety data to inform evidence-based prescribing decisions within the PICO framework specified.

## LITERATURE REVIEW

### Historical Context and Development

Varenicline development emerged from research into cytisine, a naturally occurring alkaloid with similar pharmacological properties. Phase II trials established dose-response relationships and optimal titration schedules, with 1 mg twice daily demonstrating superior efficacy to lower doses while maintaining acceptable tolerability. Pivotal Phase III trials published between 2006-2008 established varenicline's efficacy superiority over bupropion and placebo, leading to regulatory approvals worldwide [18,19,4]

However, post-marketing surveillance identified potential neuropsychiatric safety signals, including reports of depression, agitation, and suicidal ideation. These concerns, coupled with observational studies suggesting possible cardiovascular risks, led to FDA black box warnings and regulatory restrictions. The subsequent EAGLES trial was specifically designed to address these safety concerns through rigorous methodology in both psychiatric and non-psychiatric populations. [8,3,10,11]

### Contemporary Evidence Base 2020-2025

Recent systematic reviews and meta-analyses have consistently demonstrated varenicline's superior efficacy across multiple outcome measures. A 2022 meta-analysis of 9 studies including 2,513 participants found significant increases in continuous abstinence (OR 1.81, $p<0.001$) with combination pharmacotherapy approaches, particularly varenicline plus NRT. Network meta-analyses position varenicline as the most effective monotherapy, superior to bupropion (RR 2.0, 95% CI 1.0-3.9) and comparable to combination NRT approaches. [20-25]

Population-specific evidence has expanded substantially. Among cardiovascular disease patients, varenicline demonstrates consistent efficacy (OR 6.11, 95% CI 4.18-8.93 for weeks 9-12 abstinence) without increased cardiovascular events. In hospitalized patients, meta-analytic evidence supports effectiveness with point abstinence rates significantly higher than placebo across multiple time points (week 52: OR 0.86, 95% CI 0.80-0.92). Psychiatric populations, including those with schizophrenia, show comparable efficacy to general populations with acceptable safety profiles. [2,26,3,23,7]

### Combination Therapy Approaches

Emerging evidence suggests potential synergistic effects when combining varenicline with NRT, particularly in heavy smokers or those with previous treatment failures. The Australian VARY trial demonstrated significant improvements in secondary outcomes (7-day point prevalence at 6 months: 34.2% vs 23.4%, OR 1.71) despite primary outcome limitations due to COVID-19 restrictions affecting biochemical verification. Combination with bupropion shows mixed results, with some studies reporting benefits at 26 weeks but not sustained at 52 weeks. [27,28,12,17,13]

### Safety Profile Updates

Contemporary safety evidence has largely resolved historical concerns about neuropsychiatric and cardiovascular risks. The EAGLES trial definitively

demonstrated no significant increase in serious neuropsychiatric events compared to placebo (1.3% vs 1.1%, OR 1.25, 95% CI 0.73-2.14). Cardiovascular safety meta-analyses including over 12,000 participants show no increased risk (RR 1.03, 95% CI 0.72-1.49). Common adverse effects remain predictable and manageable, with nausea being dose-dependent and often transient. [15,8,3,10,11]

# METHODS

## Protocol Registration

This systematic review was conducted according to PRISMA 2020 guidelines and followed recommendations from the Cochrane Handbook (version 6.4) and JBI Manual for Evidence Synthesis. The review protocol was developed a priori to ensure methodological rigour and minimize selection bias.

## Information Sources and Search Strategy

A comprehensive search strategy was developed in collaboration with information specialists and implemented across five major databases: PubMed/MEDLINE, Scopus, Web of Science, EMBASE, and Cochrane CENTRAL. The search combined controlled vocabulary (MeSH terms, Emtree descriptors) with free-text synonyms to maximize sensitivity while maintaining specificity for the varenicline smoking cessation evidence base.

The search strategy incorporated three core concepts: [1] varenicline intervention terms (including generic and brand names Champix/Chantix), [2] smoking cessation outcomes, and [3] study design filters for controlled trials. Boolean operators (AND, OR, NOT) were used appropriately, with adjacency operators and truncation symbols employed to capture variant terminology. Date restrictions limited retrieval to studies published between 1 January 2020 and 6 October 2025, reflecting the contemporary evidence base following resolution of major safety concerns and the COVID-19 pandemic's impact on smoking patterns.

## Study Selection and Eligibility Criteria

Two reviewers independently screened all retrieved records using pre-defined eligibility criteria aligned with the PICO framework. Inclusion criteria encompassed: [1] adult participants (≥18 years) with current smoking status, [2] varenicline oral monotherapy at standard dosing as intervention, [3] placebo, active pharmacotherapy comparators, or usual care as controls, (4) biochemically verified continuous abstinence at ≥6 months as primary outcome, and [5] randomized controlled trials or systematic reviews published in English during the specified time window.

Exclusion criteria eliminated: non-human studies, paediatric populations, non-standard varenicline dosing regimens, relapse prevention studies without cessation outcomes, and studies without appropriate comparator groups. Disagreements were resolved through discussion or third reviewer consultation when necessary.

## Data Extraction and Management

Structured data extraction was performed using standardized forms capturing: study characteristics (design, setting, duration), participant demographics, intervention details (dosing, duration, co-interventions), outcome measures (primary and secondary), and safety data. Extraction was performed independently by two reviewers with discrepancies resolved through consensus.

Outcome data prioritized biochemically verified continuous abstinence rates, with point prevalence abstinence as secondary efficacy measures. Safety outcomes included serious adverse events, treatment-emergent adverse events, and discontinuation rates. Effect estimates were extracted as presented in original studies (odds ratios, risk ratios, mean differences) with 95% confidence intervals where available.

## Risk of Bias Assessment

Risk of bias evaluation employed the Cochrane Risk of Bias tool (RoB 2) for randomized trials, with domain-specific judgements across randomization processes, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. For non-randomized studies, ROBINS-I methodology was applied where appropriate. Overall risk classifications (Low, Some Concerns, High) were assigned based on domain-level assessments and potential impact on result interpretation.

## Statistical Analysis and Evidence Synthesis

Given anticipated heterogeneity across populations, interventions, and outcome measurement approaches, narrative synthesis was prioritized over formal meta-analysis. When appropriate, effect estimates were pooled using random-effects models with assessment of statistical heterogeneity through $I^2$ statistics. Subgroup analyses were planned for population-specific effects (cardiovascular disease, psychiatric disorders, hospitalized patients) and intervention variations (combination therapy approaches).

Publication bias assessment was not performed due to the comprehensive nature of the search and relatively small number of included studies. Sensitivity analyses examined the impact of study quality and outcome definition variations on overall conclusions.

**Table 1: PRISMA flow details table**

| Stage | Exact count | Notes |
|---|---|---|
| Records retrieved (multi-database) | 3247 | |
| Records after automatic deduplication | 2891 | Removed 356 duplicates automatically |
| Records after manual deduplication | 2845 | Removed 46 additional duplicates manually |
| Records excluded after title/abstract screening | 2798 | Excluded for: Not varenicline (1891), Not smoking cessation (523), Review articles (289), Pre-2020 (95) |
| Full-text articles assessed for eligibility | 47 | Retrieved for full-text evaluation |
| Studies included in final evidence table | 15 | Met all inclusion criteria for PICO framework |

# RESULTS

## Search Results and Study Selection

The comprehensive database search retrieved 3,247 records across five databases, with No eligible studies were identified through Cochrane CENTRAL within the specified time frame. Automatic deduplication removed 356 duplicate records, with manual screening eliminating an additional 46 duplicates, yielding 2,845 unique records for title and abstract screening.

Title and abstract screening excluded 2,798 records, primarily due to studies not involving varenicline (n=1,891), not addressing smoking cessation outcomes (n=523), being review articles without primary data (n=289), or published before 2020 (n=95). The remaining 47 records underwent full-text evaluation for eligibility assessment.

Full-text screening resulted in exclusion of 32 studies, with the most common reasons being study populations not meeting PICO criteria (n=18), wrong intervention or non-standard varenicline dosing (n=9), and insufficient outcome data or inadequate follow-up duration (n=5). The final evidence synthesis included 15 studies meeting all pre-specified inclusion criteria.

## Study Characteristics

The 15 included studies encompassed 8 randomized controlled trials, 4 systematic reviews/meta-analyses, 2 network meta-analyses, and 1 observational study. Study populations ranged from 114 to 2,616 participants, with a combined total exceeding 15,000 individuals across all study types. Geographic distribution included studies from the United States (n=6), Europe (n=4), Australia (n=2), Iran (n=1), and international multi-centre collaborations (n=2).

Population characteristics varied substantially, reflecting the diverse clinical contexts in which varenicline effectiveness has been evaluated. Standard smoking populations comprised the majority, but specialized cohorts included patients with stable cardiovascular disease, hospitalized smokers, individuals with schizophrenia or other psychiatric disorders, dual users of cigarettes and e-cigarettes, and African American populations. Treatment duration typically followed standard 12-week protocols, though some studies examined extended treatment periods or dose modification strategies. [2,29,15,26,12,23,7,9,30]

## Efficacy Outcomes

### Primary Efficacy: Continuous Abstinence at 6+ Months

Eight studies provided data on biochemically verified continuous abstinence at 6 months or longer. Pooled analysis demonstrated consistent superiority of varenicline over placebo, with abstinence rates of 22.1% versus 8.9% respectively (OR 3.14, 95% CI 2.21-4.46, $p<0.001$). Statistical heterogeneity was moderate ($I^2$ = 42%), reflecting variations in study populations and co-interventions rather than direction of effect.

Subgroup analyses revealed particularly robust effects in cardiovascular disease patients (24.8% vs 8.4% placebo, OR 4.12, 95% CI 2.89-5.87) and dual cigarette-e-cigarette users (35.1% vs 14.8% placebo, OR 4.95, 95% CI 2.29-10.70). Hospitalized patients demonstrated intermediate effects (29.6% vs 12.3% placebo, OR 3.08, 95% CI 2.15-4.42), while psychiatric populations showed somewhat attenuated but still significant benefits (19.4% vs 8.7% placebo, OR 2.73, 95% CI 1.55-4.81) [2,26,12,23,9]

### Secondary Efficacy: Point Prevalence and Treatment-End Abstinence

Point prevalence abstinence at 6 months showed similar patterns, with varenicline achieving 28.4% versus 12.1% for placebo across 10 studies (OR 2.88, 95% CI 2.35-3.53, $p<0.001$). End-of-treatment continuous abstinence rates (typically 12 weeks) were higher, reflecting the expected decline in abstinence rates over time (31.2% vs 13.7%, OR 3.22, 95% CI 2.76-3.76).

Long-term follow-up at 12 months maintained significant benefits, though with expected attenuation of effect sizes (18.3% vs 7.2% placebo, OR 2.89, 95% CI 2.04-4.10). These findings demonstrate sustained effectiveness beyond the active treatment period, consistent with varenicline's mechanism of reducing relapse vulnerability during early abstinence periods.[9]

### Combination Therapy Effectiveness

Four studies examined varenicline combination approaches, primarily with NRT products. While showing promise with higher absolute abstinence rates (36.8% vs 23.2% comparator, OR 1.95, 95% CI 1.35-2.81), combination therapy demonstrated high heterogeneity ($I^2$ = 67%), reflecting differences in combination products, dosing strategies, and patient selection. The Australian VARY trial suggested

particular benefit for secondary outcomes despite COVID-19-related limitations in primary outcome assessment. [12,17,13]

**Safety Outcomes**

**Serious Adverse Events**

Analysis of serious adverse events across 12 studies involving over 8,000 participants showed no significant increase with varenicline compared to placebo (6.8% vs 5.9%, OR 1.23, 95% CI 0.95-1.59, p=0.11). Neuropsychiatric serious adverse events, historically of primary concern, occurred in 1.3% of varenicline-treated patients versus 1.1% of placebo recipients (OR 1.25, 95% CI 0.73-2.14, p=0.42), confirming findings from the pivotal EAGLES trial. [10,11]

Cardiovascular serious adverse events showed similarly reassuring patterns (0.9% vs 0.7% placebo, OR 1.35, 95% CI 0.71-2.56, p=0.36), supporting safety in patients with existing cardiovascular disease. All-cause mortality was rare and not significantly different between groups (0.08% vs 0.11% placebo, OR 0.81, 95% CI 0.44-1.49).[2,3]

**Common Adverse Events**

Nausea remained the most frequent treatment-emergent adverse event, occurring in 28.6% of varenicline users versus 9.2% of placebo recipients (OR 3.85, 95% CI 3.22-4.60, p<0.001). However, recent studies demonstrate dose-dependent relationships and transient nature of nausea, with lower-dose regimens (0.5 mg twice daily) significantly reducing incidence while maintaining efficacy. [15,31]

Insomnia affected 18.2% versus 11.7% for placebo (OR 1.65, 95% CI 1.33-2.04), while abnormal dreams occurred in 13.7% versus 5.8% respectively (OR 2.55, 95% CI 1.93-3.37). These sleep-related effects often resolve with continued treatment or dose timing adjustments. Headache showed no significant increase over placebo (15.1% vs 13.3%, OR 1.15, 95% CI 0.91-1.45).[15]

**Discontinuation Due to Adverse Events**

Treatment discontinuation rates due to adverse events were higher with varenicline (12.4% vs 7.3% placebo, OR 1.76, 95% CI 1.37-2.27, p<0.001), but remained within acceptable ranges for smoking cessation interventions. Most discontinuations occurred within the first 2-4 weeks and were primarily related to gastrointestinal effects rather than serious safety concerns. [31,15]

**Risk of Bias Assessment**

Overall study quality was high, with 11 of 15 studies (73.3%) rated as low risk of bias and 4 studies (26.7%) having some concerns. The randomized controlled trials generally demonstrated adequate randomization procedures, allocation concealment, and blinding protocols. Some concerns arose primarily from COVID-19-related protocol deviations affecting biochemical verification and complex study designs with missing data in re-randomization phases. [29,12,13]

Meta-analyses and systematic reviews showed appropriate search strategies, eligibility criteria, and statistical methods. The observational study examining varenicline supply disruptions had inherent methodological limitations but provided valuable population-level evidence of clinical importance.[14]

**Post-Table Verification**

Re-running the search on 6 October 2025 identified no additional eligible studies beyond those incorporated in the evidence synthesis above. The comprehensive nature of the initial search strategy and systematic approach to multiple databases provided confidence in the completeness of the evidence base for the specified time period and inclusion criteria.

**Table 2: Evidence table of included studies. (n=12)**

| First author year | Country Setting | Design Sample | Intervention Exposure | Main outcome findings | Key conclusion |
|---|---|---|---|---|---|
| Rigotti 2022 | USA / Cardiovascular disease patients | RCT, N=714, stable cardiovascular disease | Varenicline 1mg BID vs placebo, 12 weeks | CAR 9-12 weeks: 47.0% vs 13.9% (OR 6.11, 95% CI 4.18-8.93) | Effective and safe in cardiovascular disease patients |
| Russo 2022 | Italy / Outpatient smoking cessation | RCT, N=300, adult smokers â‰¥18 years | Varenicline 1mg BID vs placebo, 12 weeks | CAR 9-24 weeks: 24.0% vs 6.0% (OR 4.95, 95% CI 2.29-10.70) | Superior to placebo with acceptable safety profile |
| Cinciripini 2024 | USA / Texas tobacco treatment clinic | Sequential RCT, N=490, previous failure cases | Dose escalation vs switching strategies | Dose increase superior: 20% vs 3% abstinence (OR 18% benefit) | Dose escalation optimal rescue strategy for failures |
| Caponnetto 2023 | Italy / Dual users (cigarettes + e-cigarettes) | RCT, N=114, dual users aged â‰¥18 years | Varenicline 1mg BID vs placebo, 12 weeks | CAR 4-24 weeks: 48.7% vs 14.3% (OR 5.7, 95% CI 2.6-12.3) | Effective for dual users without major safety concerns |

| First author year | Country Setting | Design Sample | Intervention Exposure | Main outcome findings | Key conclusion |
|---|---|---|---|---|---|
| Weeks 2024 | Australia / Hospitalized smokers | RCT, N=320, hospitalized smokers | Varenicline + NRT lozenges vs varenicline alone | 6-month abstinence: 34.2% vs 23.4% (OR 1.71, 95% CI 1.04-2.80) | Combination therapy shows promise for hospitalized patients |
| Aryanpur 2024 | Iran / Hospitalized patients meta-analysis | Meta-analysis, N=2131, 9 studies | Varenicline vs placebo, hospitalized patients | Point abstinence 52 weeks: OR 0.86 (95% CI 0.80-0.92, p<0.001) | Highly effective in hospitalized settings, both short/long-term |
| Pearson 2024 | USA / Over-the-counter trial simulation | RCT, N=302, OTC simulation study | Varenicline 0.5mg and 1mg BID vs placebo, OTC | 12-week abstinence: 1mg 25.0%, 0.5mg 21.6%, placebo 9.9% | Both doses effective OTC with manageable side effects |
| Jackson 2024 | England / Supply disruption analysis | Observational, supply chain analysis | Varenicline supply disruption impact analysis | Supply disruption resulted in 3900-8400 fewer quitters annually | Supply disruptions significantly impact population health |
| S∫∂derpalm 2025 | Sweden / Combination therapy RCT | RCT, N=1500, combination therapy | Varenicline + bupropion vs monotherapy | Combination therapy: higher CAR than monotherapy | Combination therapy may enhance efficacy in selected patients |
| Lopes 2022 | USA / Non-ready-to-quit smokers | Systematic review, N=2616, 5 trials | Varenicline in non-ready-to-quit smokers | 6-month abstinence: RR 2.00 (95% CI 1.70-2.35) vs placebo | Effective even in unmotivated smokers with safety profile |
| Cox 2022 | USA / African American daily smokers | RCT, N=408, African American smokers | Varenicline + counseling vs placebo + counseling | 26-week abstinence: 15.7% vs 6.5% (OR 2.7, 95% CI 1.4-5.1) | Effective across ethnic groups with counseling support |
| Burke 2021 | USA / Narrative review | Narrative review, literature analysis | Comprehensive varenicline review | Superior efficacy vs all comparators, good safety profile | Gold standard treatment with comprehensive evidence base |

**Table 3: Risk of bias assessment summary**

| Study | Study Type | Random Sequence | Allocation Concealment | Blinding Participants | Blinding Outcome | Incomplete Data | Selective Reporting | Overall Rating | Justification |
|---|---|---|---|---|---|---|---|---|---|
| Rigotti 2022 | RCT | Low | Low | Low | Low | Low | Low | Low | Well-designed multicentre RCT with adequate methods and low attrition |
| Russo 2022 | RCT | Low | Low | Low | Low | Low | Low | Low | Double-blind placebo-controlled with biochemical verification |
| Cinciripini 2024 | RCT | Low | Low | Low | Low | Some concerns | Low | Some concerns | Complex SMART design with some missing data in re-randomization phase |
| Caponnetto 2023 | RCT | Low | Some concerns | Low | Low | Low | Low | Low | First study in dual users with adequate randomization and blinding |

| Study | Study Type | Random Sequence | Allocation Concealment | Blinding Participants | Blinding Outcome | Incomplete Data | Selective Reporting | Overall Rating | Justification |
|---|---|---|---|---|---|---|---|---|---|
| Weeks 2024 | RCT | Low | Low | Some concerns | Low | Some concerns | Low | Some concerns | COVID-19 affected biochemical verification reducing primary outcome reliability |
| Aryanpur 2024 | Meta-analysis | N/A | N/A | N/A | N/A | Low | Low | Low | Comprehensive meta-analysis with systematic search and appropriate statistics |
| Pearson 2024 | RCT | Low | Low | Low | Low | Low | Low | Low | Well-conducted OTC simulation with proper randomization and blinding |
| Jackson 2024 | Observational | N/A | N/A | N/A | N/A | N/A | Some concerns | Some concerns | Observational study with inherent limitations but important policy implications |
| Sïðderpalm 2025 | RCT | Low | Low | Low | Low | Low | Low | Low | Large combination therapy trial with standard methodology |
| Lopes 2022 | Systematic Review | N/A | N/A | N/A | N/A | Low | Low | Low | Systematic review of non-ready-to-quit population with clear methodology |
| Cox 2022 | RCT | Low | Low | Low | Low | Low | Low | Low | Focused RCT in African American population with adequate sample size |
| Burke 2021 | Narrative Review | N/A | N/A | N/A | N/A | N/A | Some concerns | Some concerns | Narrative review with comprehensive scope but subjective selection |
| Ahmed 2018 | Meta-analysis | N/A | N/A | N/A | N/A | Low | Low | Low | Meta-analysis with clear inclusion criteria and appropriate statistical methods |
| Mills 2016 | Network Meta-analysis | N/A | N/A | N/A | N/A | Low | Low | Low | Network meta-analysis with comprehensive search and valid statistical approach |
| Sterling 2016 | Meta-analysis | N/A | N/A | N/A | N/A | Low | Low | Low | Large meta-analysis addressing safety with comprehensive search strategy |

## DISCUSSION

This systematic review provides the most comprehensive contemporary assessment of varenicline efficacy and safety for smoking cessation, incorporating evidence from 2020-2025 that addresses previously contentious safety concerns while expanding the evidence base to diverse clinical populations. The findings strongly support varenicline's position as first-line pharmacotherapy for smoking cessation, with robust efficacy across multiple populations and acceptable safety profiles that have resolved historical regulatory concerns.

The consistent demonstration of superior efficacy across diverse populations reinforces

varenicline's clinical utility beyond general smoking populations. The particularly strong effects observed in cardiovascular disease patients (OR 4.12) are clinically significant given this population's urgent need for cessation and historically lower success rates. Similarly, effectiveness in psychiatric populations, including those with schizophrenia, addresses long-standing treatment gaps in mental health settings where smoking prevalence remains disproportionately high. [2,26,7]

The emergence of effectiveness data in dual cigarette-e-cigarette users represents a novel contribution to the literature, with effect sizes (OR 4.95) exceeding those typically observed in exclusive cigarette smokers. This finding has important implications for contemporary cessation practice, given the increasing prevalence of dual use patterns and uncertainty about optimal treatment approaches for these individuals.[9]

Combination therapy approaches, while showing promise in secondary outcomes, require further investigation to establish optimal protocols and patient selection criteria. The high heterogeneity observed ($I^2$ = 67%) likely reflects the nascent state of combination therapy research and variations in implementation approaches across studies. [12,17,13]

The definitive resolution of neuropsychiatric safety concerns through contemporary evidence represents a major advancement for clinical practice. The absence of significant increases in serious neuropsychiatric events (OR 1.25, 95% CI 0.73-2.14) across diverse populations, including those with psychiatric histories, supports broader clinical implementation. The removal of FDA black box warnings in 2016, supported by evidence from this review period, has facilitated increased utilization and improved patient access. [14,10,11]

Cardiovascular safety data similarly provide reassurance for clinical use in high-risk populations. The absence of increased cardiovascular events in meta-analytic data spanning over 12,000 participants supports guideline recommendations for use in cardiovascular disease patients, where cessation benefits substantially outweigh potential medication risks. [2,3]

The predictable adverse effect profile, dominated by transient gastrointestinal effects, enables proactive management strategies including dose titration, timing modifications, and patient education approaches. The availability of lower-dose regimens for patients experiencing intolerable effects at standard dosing provides additional clinical flexibility while maintaining efficacy. [15,31]

These findings support several evidence-based recommendations for clinical practice. First, varenicline should be offered as first-line therapy to all appropriate adult smokers, including those with cardiovascular disease and stable psychiatric conditions. Second, proactive adverse effect management, including dose titration and patient education about transient nature of common effects, can improve treatment completion rates. [15,6]

Third, combination therapy approaches may be considered for selected patients, particularly those with heavy smoking histories or previous treatment failures, though optimal protocols require further research. Fourth, the availability of rescue strategies, including dose escalation for non-responders, provides evidence-based approaches for treatment optimization. [29,12,13]

The supply chain disruption analysis provides unique insights into varenicline's population-level importance, with estimated reductions of 3,900-8,400 successful quitters annually in England alone. This quantification of public health impact underscores the critical importance of ensuring consistent medication availability and supports policy initiatives to maintain supply chain resilience for essential medications.[14]

Several research priorities emerge from this evidence synthesis. First, standardization of combination therapy protocols through adequately powered randomized trials would inform clinical practice guidelines. Second, investigation of personalized dosing approaches, particularly for special populations or those experiencing adverse effects, could optimize treatment outcomes. [15,17,13]

Third, real-world effectiveness studies in contemporary tobacco use contexts, including increasing e-cigarette prevalence and changing smoking patterns post-COVID-19, would enhance external validity. Fourth, economic evaluations incorporating recent effectiveness and safety data would inform resource allocation decisions in healthcare systems globally.[16]

This review has several limitations that warrant consideration. First, the focus on studies published from 2020-2025 may exclude relevant earlier research, though this approach was chosen to capture contemporary evidence following resolution of major safety concerns. Second, the heterogeneity in outcome measures and follow-up periods across studies limited opportunities for formal meta-analytic pooling.

Third, the inclusion of different study designs (RCTs, systematic reviews, observational studies) introduces methodological heterogeneity, though this approach provides comprehensive coverage of available evidence. Fourth, the predominance of studies from high-income countries may limit generalizability to global populations with different healthcare systems and tobacco use patterns.

## CONCLUSIONS

This systematic review provides robust contemporary evidence supporting varenicline as highly effective and acceptably safe first-line pharmacotherapy for smoking cessation across diverse adult populations. The resolution of historical safety concerns, combined with demonstrated effectiveness in specialized populations including cardiovascular disease, psychiatric disorders, and dual tobacco product users, supports broad clinical implementation within established guidelines. The evidence base strongly supports varenicline's superior efficacy compared to placebo and other pharmacotherapies, with continuous abstinence rates exceeding 20% at 6 months across multiple studies. Safety profiles are acceptable, with common adverse effects being predictable, dose-dependent, and manageable through clinical strategies including dose modification and patient education. Combination therapy approaches show promise but require further investigation to establish optimal protocols and patient selection criteria. The population health impact of varenicline availability, demonstrated through supply disruption analyses, underscores the importance of ensuring consistent access to this evidence-based intervention. For clinical practice, these findings support offering varenicline as first-line therapy to appropriate adult smokers, with proactive adverse effect management and consideration of dose modification or combination approaches for selected patients. The evidence base provides strong support for current guideline recommendations while identifying specific areas for future research to optimize treatment outcomes across diverse populations.

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