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Smoking-Cessation Pharmacotherapy for Patients with Stroke and TIA: Systematic Review

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Abstract

Data regarding the efficacy and safety of smoking-cessation pharmacotherapy after stroke are lacking. We systematically reviewed data on this topic by searching Medline, Cochrane, and Clinicaltrials.gov to identify randomized clinical trials (RCT) and observational studies that assessed the efficacy and safety of nicotine replacement therapy (NRT), varenicline, and bupropion in patients with stroke and TIA. We included studies that reported rates of smoking cessation, worsening or recurrent cerebrovascular disease, seizures, or neuropsychiatric events. We identified 2 RCTs and 6 observational studies; 3 included ischemic stroke and TIA, 2 subarachnoid hemorrhage (SAH), and 3 did not specify. Four studies assessed efficacy; cessation rates ranged from 33% to 66% with pharmacological therapy combined with behavioral interventions versus 15% to 46% without, but no individual study demonstrated a statistically significant benefit. Safety data for varenicline and buopropion in ischemic stroke were scarce. Patients with SAH who received NRT had more seizures (9% vs 2%; P=0.024) and delirium (19% vs 7%; P=0.006) in one study, but less frequent vasospasm in 3 studies. In conclusion, combined with behavioral interventions, smoking-cessation therapies resulted in numerically higher cessation rates. Limited safety data may prompt caution regarding seizures and delirium in patients with subarachnoid hemorrhage.

Keywords

Cerebrovascular Disease; Stroke; Transient Ischemic Attack (TIA); Secondary Prevention; Smoking Cessation; Pharmacology

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Introduction

Eighteen percent of patients hospitalized with stroke nationwide are current smokers, and the proportion exceeds 40% among young patients with stroke [1, 2]. Smoking is associated with worse outcomes, including recurrent stroke and mortality, after ischemic stroke, transient ischemic attack (TIA), and subarachnoid hemorrhage (SAH) [3–6] However, smoking cessation within 6 months of ischemic stroke and transient ischemic attack (TIA) has been associated with a markedly reduced long-term risk of vascular events and death [7].

The efficacy of nicotine replacement therapy (NRT), bupropion, and varenicline for smoking cessation in the general population is established [8]. This is not the case for patients with cerebrovascular disease. The American Heart Association/American Stroke Association (AHA/ASA) secondary prevention guidelines assert that smoking-cessation pharmacotherapy is effective in general, while acknowledging that data from patients with stroke and TIA are unavailable [9]. The AHA/ASA Guidelines for the Early Management of Patients with Acute Ischemic Stroke were recently updated to include recommendations regarding the use of select pharmacotherapies;[10] however, the cited data are sparse and largely drawn from studies of the general population. In contrast, abundant data specific to patients with cardiovascular disease informed the recent American College of Cardiology endorsement of smoking-cessation pharmacotherapy for patients hospitalized with cardiovascular disease[11].

Efficacy and safety findings from patients with cardiovascular disease[12–14] may not be generalizable to stroke and TIA. Patients with stroke may have higher rates of spontaneous, un-aided cessation from stroke-related attenuation of nicotine dependence and stays in smoke-free rehabilitation environments[15–20]. Further, these patients pose unique safety considerations related to vulnerability to cerebral ischemia,[21–23] seizures,[24, 25] and neuropsychiatric symptoms[26, 27]. In light of these considerations, we performed a systematic review to evaluate the evidence for efficacy and safety of smoking-cessation pharmacotherapy in patients with stroke and TIA.

Methods

We conducted a systematic review of randomized clinical trials and observational studies that investigated the efficacy and safety of smoking-cessation pharmacotherapy for patients with stroke and TIA. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards[28]. We reviewed only previously published data; institutional review board approval and individual patient informed consent were not required.

Search Strategy

We queried the Medline, Cochrane Library, and clinicaltrials.gov databases last on October 23, 2019. We adapted a published search strategy [12] to retrieve studies regarding cerebrovascular disease (Supplemental Material). We additionally reviewed references of included articles and relevant reviews. Search results were exported into a web-based systematic review software (Covidence, Veritas Health Innovation, Melbourne, Australia).

Study Selection

Two independent reviewers (NSP, SSO) screened titles and abstracts. Articles selected by at least one reviewer were selected for full-text review by both reviewers; consensus and a tie-breaker (JW) were used to select the final articles. Study selection criteria were established *a priori*; restrictive criteria were not used given the suspected paucity of data on this topic. We included both randomized trials and observational studies that compared pharmacological intervention(s) (NRT, varenicline, and bupropion) to a non-pharmacological or non-interventional control, in addition to single-arm observational studies. Studies that used behavioral co-interventions alongside pharmacological therapy were included. We limited studies to those that included only, or separately reported adequate subgroup data for, adult patients with stroke and TIA. We included all stroke types to maximize scope. Studies that reported either the efficacy outcome of smoking cessation or at least one safety outcome were included. Pre-specified safety outcomes were: recurrent or worsening cerebrovascular disease, death, clinical outcomes, seizures, and neuropsychiatric events. We excluded single case reports and unpublished abstracts. Only articles published in English were included.

Data Abstraction

After a standardized data form was created and iteratively revised, two reviewers (NSP, SSO) independently abstracted data. After collation, discrepancies were resolved by consensus and through discussion with an additional reviewer (JW). Study characteristics were country, design, setting, publication year, study population characteristics, number of patients, and duration of follow-up. Patient characteristics were demographics, type of cerebrovascular disease, and smoking duration and frequency. We recorded the nature, dose, duration, and behavioral co-interventions for pharmacological interventions. We recorded the number of patients with self-reported or biochemically-validated smoking cessation, with preference given to biochemically-validated cessation rates. We additionally abstracted the number of patients experiencing each adverse outcome.

Study Quality Assessment

Two reviewers (NSP, SSO) independently rated the overall quality of evidence by outcome of interest using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach[29]. This approach allows joint consideration of data from heterogeneous study designs (randomized clinical trials and observational studies) for each individual outcome while simultaneously considering overall design quality, consistency of findings, directness, precision, strength of association, and bias in individual studies. The overall quality is described as “very low”, “low”, “moderate”, and “high”.

Synthesis of Results

We calculated pooled frequencies where possible for the outcomes of smoking cessation and individual adverse events. However, after completion of study selection, we decided not to perform statistical between-group comparisons or a formal, quantitative meta-analysis given the marked heterogeneity in study designs, populations, and nature of interventions and outcomes in the available studies.

Data Availability

Our detailed search strategy is available in Table I and Table II of the Supplemental Materials. All data included in this review are available in Tables 1 and 2.

Results

The search identified 452 potentially relevant publications, of which 8 met inclusion criteria (Figure). We identified 2 randomized trials and 6 observational studies (Table 1). Of the 8 studies, 3 included patients with ischemic stroke and TIA, 3 included SAH, and 2 did not specify. A total of 1,506 patients with cerebrovascular disease were included: 279 ischemic stroke or TIA, 580 SAH, and 647 stroke not specified. Study settings included intensive care units (3), inpatient wards (2), outpatient clinics (2), and unspecified (1). Readiness to quit was assessed in 3 studies. Pharmacological interventions were NRT in 4 studies, a choice of varenicline or bupropion in 1 study, and a choice of NRT, varenicline, or bupropion in 1 study. A total of 1,068 (71%) patients were randomized to or received pharmacotherapy-containing cessation interventions. In 4 studies, a behavioral co-intervention of variable intensity was provided, and 4 studies were observational without a specified control intervention. Rates of smoking cessation were reported in 4 studies; 2 studies reported biochemically validated rates. Mortality was reported in 2 studies, clinical outcomes in 1 study, recurrent or worsening cerebrovascular disease in 4 studies, seizures in 1 study, and neuropsychiatric events in 1 study. The duration of follow-up ranged from the index hospitalization only to up to 1 year.

Efficacy

We did not identify any randomized, placebo-controlled, double-blinded trials that evaluated the efficacy of a pharmacological intervention in patients with cerebrovascular disease. Two pilot studies randomized patients with ischemic stroke or TIA to interventions that included cost-free pharmacological therapy[30, 31]. In one study, 28 patients received counselling and were randomized to cost-free pharmacotherapy or a standard prescription for pharmacotherapy; a nominally higher proportion of patients given cost-free pharmacotherapy used and was compliant with medication, and these patients had a non-significantly higher odds of abstinence[30]. In the second study, 94 patients were randomized to a 30-minute individual counseling session or an intensive intervention comprised of a 5-session program and free NRT[31]. Again, patients randomized to receive the intensive intervention had a non-significantly higher rate of cessation. In both, the lack of blinding conferred a high risk of bias.

We also identified an observational study of 157 Korean men with ischemic stroke that assessed smoking cessation in a before-after analysis of an intensive behavioral intervention that included consideration for pharmacotherapy (varenicline, bupropion, or NRT)[32]. Patients in the intervention period had three times the odds of smoking cessation compared to those treated in the standard of care period; however, they did not find that use of pharmacotherapy was itself associated with smoking cessation. In these pilot randomized trials and one observational study, cessation rates ranged from 33% to 66% with interventions including pharmacotherapy or cost-free pharmacotherapy versus

15% to 46% without, without any statistically significant differences between approaches in any individual study. In aggregate, of the 150 patients who received interventions including pharmacotherapy or who were randomized to interventions that included cost-free pharmacotherapy, 83 (55%) quit smoking. Of the 129 patients in control groups, 52 (40%) quit smoking. Excluding the trial comparing cost-free versus standard of care prescriptions, [30] 78 (58%) of 135 patients in pharmacotherapy groups versus 50 (43%) of 116 patients in non-pharmacotherapy groups quit smoking. For comparison, in an analysis of a nationwide smoking-cessation program from Turkey that reported rates of 1-year cessation among patients with a prior stroke not further specified, 34% of patients taking a cessation aide quit smoking[33]. Overall, the quality of evidence for smoking cessation efficacy was “very low” by the GRADE criteria (Table 2).

Safety

Studies reporting smoking-cessation rates did not report adverse events, and no safety studies for patients with ischemic stroke and TIA were identified. A registry-based, self-controlled study of NRT reported that the risk of first stroke, not further specified, was not increased after prescription of an NRT[34]. With regards to the safety endpoint of recurrent or worsening cerebrovascular disease, they performed a secondary analysis of recurrent stroke and reported that the risk of recurrent stroke was not increased after prescription of an NRT, but they did not provide measures of effect. Two single-center, observational studies of NRT in patients with SAH reported rates of vasospasm[35, 36]. An additional study included patients with SAH alongside other patients admitted to a neurosurgical intensive care unit and adjusted for presence of SAH when examining the association between NRT and vasospasm[37]. Rates of angiographic vasospasm were similar in patients with SAH receiving and not receiving NRT in individual studies. In aggregate, vasospasm was seen in 72 (27%) of 263 patients receiving NRT and 117 (38%) of 304 patients not receiving NRT. In two studies of patients with SAH reporting clinical vasospasm rates,[35, 36] vasospasm was observed in 49 (23%) of 215 patients receiving NRT and 80 (29%) of 277 patients not receiving NRT. One study adjusted for Fisher grade and found NRT was associated with less clinical vasospasm (odds ratio [OR], 0.45; 95% confidence interval [CI], 0.23-0.88)[35]. Last, one study reported that rates of delayed cerebral ischemia did not differ between patients receiving (25%) and not receiving (23%) NRT (P=0.65)[36]. Overall, we deemed evidence regarding recurrent or worsening cerebrovascular disease to be moderate in quality by the GRADE criteria (Table 2).

Data regarding mortality, clinical outcomes, seizures, and neuropsychiatric adverse events were scarce. In one study of patients with SAH, NRT was associated with a lower odds of 3-month mortality after adjusting for age, cerebral edema, and SAH grade (OR, 0.12; 95% CI, 0.04-0.39)[36]. A separate study of patients with SAH reported a nominally lower rate of in-hospital mortality among those who received NRT (2% versus 7%)[35]. This study also reported that NRT-treated patients were more likely to have a good functional outcome at discharge (Glasgow Outcome Scale score <4) after adjusting for clinical severity and grade (OR, 2.17; 95% CI, 1.19-3.97). A single study of patients with SAH reported both higher rates of seizures (9% vs 2%; P=0.024) and delirium (19% vs 7%; P=0.006) among patients

receiving NRT[36]. The quality of data for each of these outcomes was “very low” by the GRADE criteria (Table 2).

Discussion

Data supporting the efficacy and safety of smoking-cessation pharmacotherapy in patients with acute cerebrovascular diseases are limited and of generally low quality. Numerically higher rates of smoking cessation were observed among patients given interventions that included pharmacotherapy, albeit in combination with intensive behavioral therapy. Safety data were scarce, except for data suggesting no increase, and potentially a decrease, in rates of vasospasm among patients with SAH treated with NRT. A single study raised the possibility of higher rates of seizure and delirium in these patients.

Prior reviews on this topic differed in scope by including studies of behavioral, non-pharmacological interventions and not reporting safety data[38] or restricting inclusion to studies of NRT in patients with SAH[39]. In this systematic review, we comprehensively evaluated efficacy and safety data for smoking-cessation pharmacotherapy in patients with stroke and TIA in a framework informed by considerations specific to this population. Whereas randomized, placebo-controlled trials have assessed the efficacy and safety of bupropion and varenicline for patients with cardiovascular diseases including acute coronary syndrome,[14, 40–43] no such data exist for patients with stroke and TIA. A registered randomized study of NRT in patients with SAH (NCT02350335) has not yet been published and will not be informative regarding other therapies or for other forms of stroke. In contrast to patients with cardiovascular diseases, patients with stroke and TIA uniquely experience reductions in nicotine dependence from insular and basal ganglia injury[17, 18, 44]. Whether NRT or varenicline, which is a partial nicotine receptor agonist, provide additional reductions in dependence and smoking urges in patients with mesolimbic pathway disruption is unknown. Further, patients with stroke often have prolonged admissions in smoke-free environments, such as inpatient rehabilitation centers, and studies of patients with cardiovascular disease have found that longer length of stay and participation in cardiac rehabilitation facilitate smoking cessation[20, 45]. These biological and care-related factors may result in spontaneous cessation rates that are higher than in the general or cardiovascular disease population, such that the benefit of pharmacotherapy may be reduced. Demonstrating the efficacy of cessation pharmacotherapy for patients with stroke and TIA is necessary to establish effective, standardized approaches for secondary prevention both in the acute and chronic settings.

With the exception of data regarding vasospasm in patients with SAH, which had previously been noted,[39] safety data in patients with stroke or TIA are limited. There are several important safety concerns that remain unaddressed by the current literature. First, bupropion increases the risk of seizures[25] and is formally contraindicated in patients at risk of seizures. The package insert for varenicline was also recently updated to reflect post-marketing observations of seizures[46]. Stroke, particularly hemorrhagic stroke, is associated with an increased risk of seizures[24]. Whether bupropion and varenicline are associated with an excess risk of seizures in patients with recent or any prior stroke is unknown. Second, although the Evaluating Adverse Events in a Global

Smoking Cessation Study (EAGLES) demonstrated that varenicline was safe in patients with a prior history of chronic psychiatric comorbidities,[47] it is unclear whether these data are applicable to patients with stroke, who face an increased risk of suicide[26, 27]. Third, a randomized clinical trial suggested that varenicline was safe for use in patients with acute coronary syndrome[14]. However, this study was not powered for safety outcomes, and a large observational study found varenicline use to be associated with an increased risk of cardiovascular events[48]. The American College of Cardiology cites these data in tempering their recommendations regarding in-hospital initiation of varenicline after acute coronary syndromes[43]. Whether varenicline can safely be initiated during hospitalization for stroke and TIA, to ideally achieve therapeutic levels by the time of discharge, is unknown. Last, animal data suggest that nicotine may increase infarct size and cerebral edema after stroke,[21–23] which raises concerns regarding in-hospital initiation of NRT after ischemic stroke. Determining the cerebrovascular safety profile of cessation pharmacotherapy is necessary before making strong recommendations, especially with regards to in-hospital initiation after acute ischemic stroke and TIA.

The strengths of this systematic review include *a priori* specification of safety outcomes of interest, a robust search strategy, and broad inclusion criteria. This approach resulted in substantial heterogeneity, precluding a formal quantitative meta-analysis, but permitted a comprehensive overview of cessation pharmacotherapy efficacy and safety data. The results remain hypothesis-generating. However, we have outlined areas of interest that deserve further pharmacoepidemiological or randomized study.

Conclusions

There were insufficient high-quality data to conclusively assess the efficacy and safety of smoking-cessation pharmacotherapy in patients with stroke and TIA. More data specific to this patient population are ideally needed in order to make strong recommendations regarding the use of smoking-cessation pharmacotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures:

Dr. Elkind serves as the Chairman of the Advisory Committee to the American Stroke Association and on the National, Founders Affiliate, and New York City boards of the American Heart Association. He receives royalties for chapters on stroke from UpToDate. Dr. Parikh, Dr. Salehi Omran, Dr. Kamel, and Dr. Willey: none.

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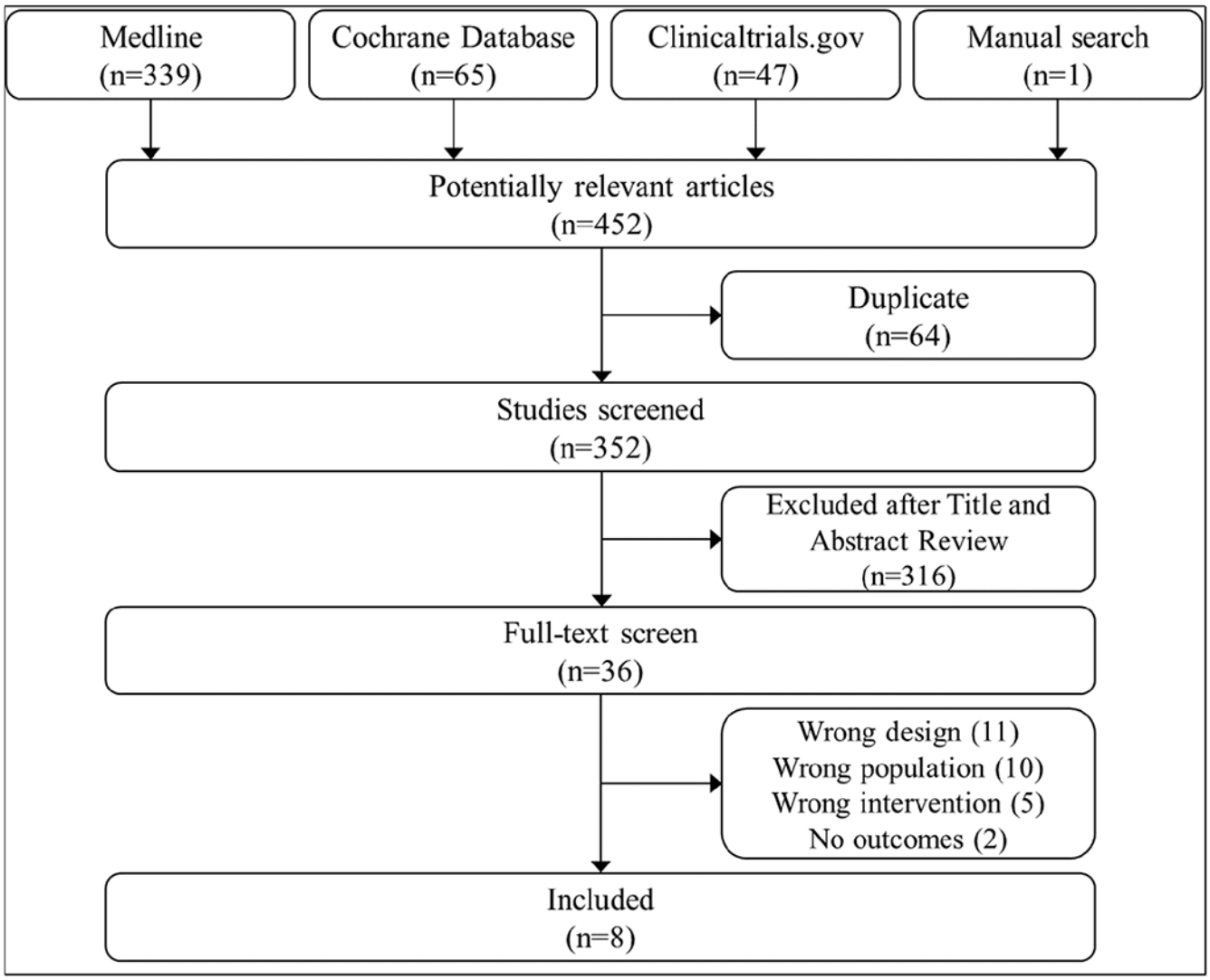

Figure.

Study selection flow diagram.

Two reviewers independently screened titles and abstracts and then full-text manuscripts prior to including 8 manuscripts in this systematic review.

Table 1.

Summary of Included Studies

1st author	Year	Design	Population/Setting	Pharmacotherapy	Co-intervention	Number of patients (n)*			Efficacy Outcome(s)	Safety Outcome(s)
						Total	Rx.	Control		
Frandsen	2012	Randomized trial	IS, TIA In-patient	Free NRT	Intensive behavioral intervention	94	49	45	6-mo. cessation, self-reported and exhaled CO	None
Papadakis	2011	Randomized trial†	IS, TIA Clinic	Free NRT, bupropion, varenicline	Behavioral intervention	28	15	13	6-mo. continuous and 7-day point abstinence (exhaled CO)	None
Lee	2005	Observational	IS In-patient	NRT, bupropion, varenicline	Intensive behavioral intervention	157	86	71	1-year sustained and 1, 3, 6, 9, 12 mo. point abstinence	None
Çelik	2015	Observational	Stroke Community	Bupropion, varenicline	Support program	141	141	N/A	1-year smoking status	None
Carandang	2011	Observational	SAH ICU	NRT patch	None	258	87	171	None	Vasospasm‡, DCI, seizures, delirium, 3-month mortality
Seder	2011	Observational	SAH ICU	NRT patch	None	234	128	106	None	Vasospasm‡, in-hospital mortality, Glasgow Outcome Scale
Panos	2010	Observational§	SAH ICU	NRT patch	None	88	56	32	None	Vasospasm
Hubbard	2005	Observational‖	Stroke Community	NRT	N/A	506	506	N/A	None	Recurrent stroke

Abbreviations: Rx, pharmacotherapy; IS, ischemic stroke; TIA, transient ischemic attack; NRT, nicotine replacement therapy; CO, carbon monoxide; SAH, subarachnoid hemorrhage; ICU, intensive care unit; DCI, delayed cerebral ischemia.

*For studies that included patients with and without cerebrovascular disease, the numbers reported here are only for subgroups with cerebrovascular disease.

†Randomized patients to a cost-free pharmacotherapy or provision of a prescription for pharmacotherapy. More patients in the cost-free group initiated and complied with pharmacotherapy.

‡Rates of angiographic and clinical vasospasm were reported.

§This study included patients admitted to a neurosurgical ICU. Only data for patients with SAH were included for this systematic review. We assumed that all of the reported occurrences of vasospasm occurred in patients with SAH.

‖This study evaluated the risk of stroke after NRT prescription; in a secondary analysis, the outcome was recurrent stroke among patients with prior stroke. Only data pertaining to the latter analysis were included here.

Table 2.

GRADE Quality Assessment of Included Studies and Summary of Findings, By Outcome of Interest

Studies	Design Quality	Study Quality	Consistency	Directness	Other Factors*	Overall Quality†	Summary of Findings
Efficacy – Smoking Cessation							
Frandsen Papadakis Lee Çelik	Low quality – pilot RCTs and observational data	No additional serious limitations	No important inconsistency	Uncertainty: co-interventions and non-distinct control group	Sparse data and high risk of bias in non-blinded randomized trials	Very low	Numerically increased cessation in individual studies with interventions including pharmacotherapy
Safety – Recurrent or Worsening Cerebrovascular Disease							
Seder Carandang Panos Hubbard	Low quality – observational	No additional serious limitations	No important inconsistency	No uncertainty about directness	No other major limitations, and +1 level for strength of associations	Moderate	Less vasospasm with NRT, after adjusting for Fisher grade. DCI rates similar. Recurrent stroke not increased with NRT in one study.
Safety – Mortality							
Seder Carandang	Low quality – observational	No additional serious limitations	No important inconsistency	No uncertainty about directness	Sparse data	Very low	Less in-hospital mortality and 3-month mortality (after adjusting for age, cerebral edema, grade) with NRT.
Safety – Clinical Outcomes							
Carandang	Low quality – observational	No additional serious limitations	Data too sparse to assess consistency	Uncertainty: outcome measure	Sparse data	Very low	More good functional outcomes at 3 months with NRT, after adjusting for severity and grade.
Safety – Seizures							
Seder	Low quality – observational	No additional serious limitations	Data too sparse to assess consistency	Uncertainty: outcome measure	No other major limitations	Low	More seizures with NRT in single observational study.
Safety – Neuropsychiatric Events (Delirium)							
Seder	Low quality – observational	No additional serious limitations	Data too sparse to assess consistency	Uncertainty: outcome measure	No other major limitations	Low	More delirium with NRT in single observational study.

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized clinical trial; NRT, nicotine replacement therapy; DCI, delayed cerebral ischemia.

*Other factors are: imprecision/sparse data, strength of association, bias, dose-response gradient, possibility of residual confounding.

†Overall quality determined after iteratively up- or down-grading quality based on study quality, consistency, directness, and other factors, after assigning an initial quality rating based on design quality.