The Effectiveness of Smoking Cessation Interventions in Smokers with Cerebrovascular Disease: A systematic review and meta-analysis.

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The Effectiveness of Smoking Cessation Interventions in Smokers with Cerebrovascular Disease: A systematic review and meta-analysis.

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Abstract

Objective: The main objective of this study was to determine the effectiveness of smoking cessation interventions in increasing cessation rates in smokers with cerebrovascular disease.

Design: Systematic review and meta-analyses. Two independent reviewers searched information sources and assessed studies for inclusion/exclusion criteria.

Eligibility criteria for included studies: Randomized control trials published prior to the 31st December 2011 investigating smoking cessation interventions in smokers with cerebrovascular disease were included. No age or ethnicity limitations were applied to be as inclusive as possible.

Methods: We followed the PRISMA statement approach to identify relevant randomized control studies. We used a mixed effects Mantel-Haenszel approach meta-analysis to pool estimate effects for randomized control trials.

Results: Of 852 identified articles, 4 articles fit the inclusion criteria describing the outcome in 303 patients. The overall cessation rate with a smoking cessation intervention was 28.1% (42/153) while without one was 24.7% (37/150). However, the meta-analysis revealed a non-significant effect of using a smoking cessation intervention on quitting (RR 1.19; 95% CI 0.81 to 1.73; p=0.38, I^2=0.00).

Conclusions: There is a dearth of intervention studies that explore this area of secondary stroke prevention. Furthermore, of those intervention studies that were found, only two implemented evidence based approaches to smoking cessation. More studies are needed to determine how effective SCI's are in increasing cessation rates in this high risk population of smokers.

ARTICLE SUMMARY

Article focus

- To asses the effectiveness of smoking cessation interventions in smokers with cerebrovascular disease.

Key messages

- There is a limited number of intervention studies that explore this area of stroke prevention.

- Of those intervention studies found, only a handful employed evidence based approaches to smoking cessation.

- The review was underpowered to achieve statistically significant results.

Strenghts and limitations of this study

- This is the first review to explore the effectiveness of stop smoking interventions in this high risk group of smokers.

- This review explores the breadth of potential interventions in stroke and TIA patients.

- Limitations of this study include a small number of available of studies, large heterogeneity in population, intervention and outcome.

Introduction

Smoking prevalence has decreased in the United States over the last 40 years and as of 2009 approximately 46 million people, or 20.6% of all adults (aged 18 years and older), in the United States smoke cigarettes.[1] It is estimated that over a quarter of all strokes can be attributed to smoking.[2] Large epidemiological cohort studies have demonstrated that cigarette smoking is a major independent risk factor for ischemic stroke. [3, 4, 5]

The Framingham Heart Study demonstrated that heavy smokers (>40 cigarettes/day) were twice as likely to have a stroke compared to light smokers (< 10 cigarettes/day). [3] The risk of stroke decreased after two years of smoking cessation and was at the level of a non-smoker after five years of quitting. [3]

A meta-analysis of thirty-two studies found an increase of 50% relative risk [RR] of strokes (95% confidence interval [CI] 1.4 to 1.6) was associated with cigarette smoking. [4] These studies provide support to the benefits of smoking cessation in patients with cerebrovascular disease. The risk of stroke declines soon after cessation among smokers regardless of age.[5] The data from observational studies have led to the general acceptance of the benefit of smoking cessation in stroke prevention. There is a lack of interventional studies and what is less established is the relative benefit of smoking cessation interventions (SCI's) in the stroke population.

It is unclear if the effectiveness of these strategies translates to a population with cerebrovascular disease who may have motor, language or cognitive disability. The purpose of this systematic review is to present up-to-date information regarding the effectiveness of SCIs in increasing cessation rates in patients with established cerebrovascular disease.

Methods

Data sources

Studies were identified from MEDLINE (1980 to Present), EMBASE (1980 to Present) and CENTRAL (May 22, 2012) databases. The following MeSH terms were used to search the MEDLINE database: "smoking cessation", "stop or quit or cease or cessation", "cerebrovascular disorders", " brain ischemia", "transient ischemic attack", "brain or cerebral", "brain hemorrhage", "brain or intracranial", "cerebrum or cerebral", "stroke", " brain embolism and occlusive cerebrovascular disease". Similar terms were used for EMBASE and CENTRAL databases.

Study selection

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[6] for randomized control trials. We included studies if: 1) patients were diagnosed with cerebrovascular disease by a physician or neurologist. 2) We applied no ethnicity or age limitations in order to be as inclusive as possible. 3) We also included studies that reported smoking cessation intervention conditions (behavioural, pharmacotherapy, combination therapy). 4) Finally we excluded studies that did not report cessation rates.

Data extraction

We used a standardized form completed by two reviewers (RE, NB) independently and in duplicated extracted data from selected articles. We resolved discrepancies by consensus. Extracted data consisted of study characteristics (first author, year publication), patient

characteristics (mean age, number of smokers, type stroke diagnosis), type of SCI (behavioural, pharmacotherapy, combination), length of follow-up of the intervention and cessation rates.

Outcome of interest

The main outcome of interest was the number of patients who quit smoking either using a smoking cessation intervention versus those who did not.

Quality of assessment of primary studies

We appraised selected articles for their methodological quality and bias using the Jadad scale.[7] The Jadad scale takes into account several methodological characteristics of clinical studies such as blinding, randomization and dropouts.[7] Scores less than 3 were considered as low quality.

Statistical Analysis

We used a mixed model Mantel-Haenszel meta-analysis approach to combine pooled effect estimates and 95% CI's were calculated. The I^2 test was used to determine whether there was statistical heterogeneity between individual studies. Comprehensive meta-analysis 2.0 statistical software was used for the analyses.

Results

Effect of SCI on long-term quit rates

Of 852 articles identified, 4 articles were deemed to fit the inclusion criteria. Characteristics and flow of included studies can be found in Table 1 and Figure 1 respectively. The mean age of smokers was 66.5 (+/- 12.5). An overall Jadad score of the selected papers was 3.75 out of a possible score of 5. With an intervention, 42 of 153 smokers quit versus 37 of 150 in the control group. This results in an overall cessation rate of 28.1% for the intervention group compared to 24.7% for the control group. The meta-analysis revealed a non-significant effect of using a SCI on quitting (RR 1.19; 95% CI 0.81 to 1.73; p=0.38, I^2=0.00) (Figure 2).

Results of individual studies and risk of bias across studies

The first study explored the role of a patient and general practitioner systematic follow-up intervention to improve risk factor management after stroke.[8] The study recruited 523 consecutive incident stroke survivors of which 154 (29.4%) patients were identified as smokers at baseline. They were then randomized into the control (n=78) and intervention group (n= 76). The overall intervention involved providing tailored evidence-based management advice to general practitioners, patients, and caregivers post-stroke. The advice consisted of treatment with antihypertensive therapy, treatment with antiplatelet therapy, and smoking cessation. Smoking cessation advice was provided in regards to nicotine replacement therapy (NRT) use .[8] The authors found that at 1 year, 21/76 (27.6%) patients in the intervention group who received smoking cessation advice in regards to NRT quit smoking. In the control group at 1 year, 22/78 (28.2%) patients successfully quit smoking.[8]

The second study explored the impact of a stroke nurse specialist's input on risk factor modification. [9] The population was selected from a clinic of ambulant patients with a diagnosis of stroke or TIA who were attending for on-going rehabilitation in a UK teaching hospital. There were 205 patients recruited of which 78 patients were identified as smokers (38%). There were 36/100 (36%) patients that were randomized into the intervention group and 42/105 (40%) were randomized into the control group. Of those randomized into the intervention group, 13/49 (26.5%) were identified as smokers. Of those randomized in the control group, 14/53 (26.4%) were identified as smokers. The intervention consisted of meetings at 3 month intervals with a

stroke nurse specialist to discuss modification of lifestyle (diet, exercise or increased activity, smoking). The control group received usual care from medical staff.[9] Upon review of this paper, it was noted that cessation rates in the original paper were not reported. We consulted the principal investigator and cessation rates are reported here from a 3 year follow-up study from McManus and associates from the original cohort.[10] Reported cessation rates in the intervention group at 42 months was found to be 1/13 (0.07%).[10] None had quit in the control group (0/14).[10]

The third study was a pilot trial of standardized counseling and cost-free pharmacotherapy for smoking cessation in secondary stroke prevention.[11] Patients who have recently experienced a TIA or stroke or have been identified as being at high risk for a cerebrovascular event were recruited and were randomized to either cost-free (CF) intervention or prescription (P) control group. Patients randomized in the CF group received free of cost medications along with counseling with a smoking cessation nurse for 26 weeks.[11] There were 255 smokers were identified and 28 participants were enrolled based on readiness to quit. The control group received usual care and prescriptions to pharmacotherapy. Cessation rates at 26 weeks for the intervention and control group was 4/15 (26.6%) and 2/13 (15.4%) respectively.[11]

The fourth study examined the difference between a minimal versus intensive smoking cessation intervention in increasing cessation rates in recruited patients with a recent stroke or TIA.[12] There were 94 smoking patients with a recent stroke or TIA that were recruited for this study.[12] For the purpose of this review and meta-analysis, the minimal smoking cessation intervention was considered as the control group while the intensive smoking cessation intervention was regarded as the intervention group. The control group consisted of a 30 minute counseling session with the study nurse advising patients to quit smoking.[12] A total of 45 patients were randomized into the control group.[12] The intervention group received five sessions of

smoking cessation counseling with the study nurse while receiving free NRT.[12] A total of 49 patients were randomized into the intervention group.[12] Cessation rates at 6 months for the intervention and control group was 13/45 (28.9%) and 16/49 (32.7%) respectively.[12]

The methodological quality of each study scored collectively 3.75 out of 5 on the Jadad scale. There were some limitations to each study. Sample size was an issue in all of the included studies. For example the small number of participants (n = 28) in Papadakis et al.'s study meant that the study was relatively underpowered.[11] Similarly, a limited number of patients (n=94) recruited in the Frandsend et al.'s study saw little effect of the intensive smoking cessation intervention.[12] A larger trial would be needed to further explore the favourable trend documented in both studies. Furthermore, the provision of pharmacotherapy, counseling and follow-up may be an enhancement to 'real world' standard of care experienced by TIA and stroke patients. A similar underpowered result due to a small sample size was observed in the study by Ellis et al./McManus et al. [9, 10] They noted that the risk factor control in the control group was better than anticipated from pilot studies and in comparison to other trial evidence. In regards to study design, Ellis and associates[9] implemented only a single blind randomization design while Wolfe and colleageus[8] and Papadakis and associates[11] implemented a cluster randomized design for their studies. It is generally accepted that the gold standard in randomized control studies lie in a double-blind randomization design which was implemented by only Frandsend et al.[12] Finally, all included studies recruited patients from fairly homogenous sources such as 2 GP clinics,[8] hospitals[9, 12] and a single stroke clinic,[11] which may not be generalizable to a broader stroke population in other settings.

Discussion

The purpose of this systematic review was to determine the effectiveness of SCIs in increasing cessation rates in patients with established cerebrovascular disease.

Our results demonstrate that there was a dearth of interventional studies that explore this area of stroke prevention which may have contributed to the lack of statistical significance in our meta-analyses. Furthermore, there seems to be a lack of evidence based implementation of proven SCIs. There is a link between sub-optimal use of evidence based smoking cessation medications and pharmacotherapy to poorer rates of smoking abstinence.[11] We found that only two of the four interventional studies[11,12] implemented evidence based approaches to smoking cessation. The approach that these studies took fell in line with recommendations outlined in the *Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update.*[13]

Fiore and associates[13] suggested that effective smoking interventions consist of pharmacotherapy coupled with counseling and follow-up. First line pharmacotherapy such as NRT, Buproprion and Varenicline can double or even triple the likelihood of long-term smoking abstinence for heavy smokers (who consume > 10 cigarettes per day) when coupled with behavioural counseling and follow-up.[14-16]

Smoking cessation interventions have been demonstrated to be effective in other populations in particular patients with coronary heart disease (CHD). CHD patients can benefit up to an increase of 44% in their cessation rate success.[17] A decrease of the risk of mortality and non-fatal myocardial infarction by 32% and 36% respectively has also been observed using this approach.[18] Larger clinical studies need to employ evidence based approaches to smoking cessation to determine their effectiveness in smokers with cerebrovascular disease.

There are several limitations in the present study which should be considered in any interpretation of the findings. There was a high degree of heterogeneity among pooled data for the meta-analysis in regards to the population, intervention and outcome. There was significant variability in the population of the included studies. For example, an array of stroke diagnoses was found ranging from incident stroke and TIA. Pooled interventions also varied between studies ranging from non-specific advice on quitting and pharmacotherapy use to more specific interventions that involved the use of NRT, counseling and follow-up. The duration of interventions was also different amongst the included studies ranging from 3 to 42 months follow-up. Finally cessation was only quantified biochemically by only two studies. [11, 12] Wolfe and associates[8] used both biochemical assays along with self-reported smoking status to quantify cessation. However, these authors only used the biochemical assays to determine the amount of misreporting in self-reported data and did not correct misreported smoking status.[8] Ellis and colleagues did not report how cessation was quantified.[9]

Conclusion

The paper provided results from a systematic review that explored the effectiveness of SCI's in increasing cessation rates. Evidence was found regarding the lack of interventional studies that explore this area of secondary stroke prevention. Furthermore, of those interventional studies that were found, only two studies implemented evidence-based approaches in smoking cessation. Larger studies are needed to determine how effective SCI's are in increasing cessation in smokers with established cerebrovascular disease.

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Contributorship statement: R. Edjoc performed primary drafting of the manuscript along with data extraction and analyses. R. Reid formulated the research question and provided feedback on the manuscript. M. Sharma provided feedback on the drafted manuscript.

Data Sharing Statement: There is no additional data available.

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Figure 1: Exclusion criteria and paper selection procedure

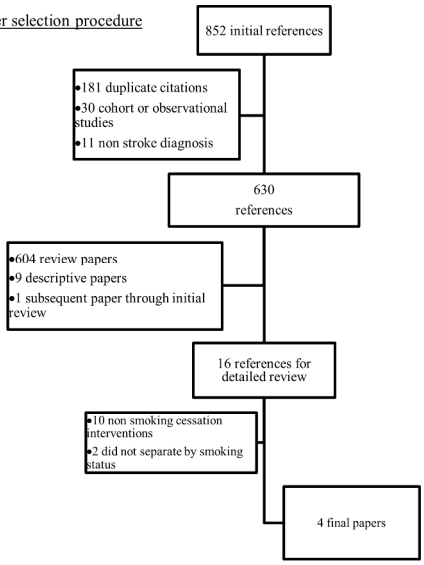

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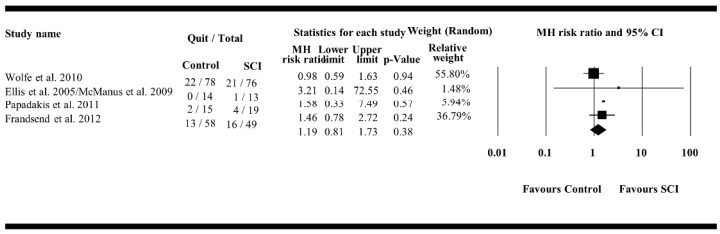
Figure 2: Meta-analysis of included studies



254x190mm (300 x 300 DPI)

Table 1: Characteristics of included studies

Study identification	Type of SCI/Control	Patient Characteristics	Jadad score	Cessation rate
Wolfe et al. 2010[8]	SCI: Advice on NRT use Control: Usual care Follow-up: 1 year	Mean age: 45% over 80 yrs.Gender: 47% female Nsmokers= 154 (stroke survivors) Nintervention =76 Ncontrol =78	3	Nintervention =21/76 (27.6%) Ncontrol = 22/78 (28.2%)
Ellis et al. 2005/McManus et al. 2009 [9, 10]	SCI: Discussion with nurse specialist on lifestyle modification in regards to smoking cessation Control: Usual care Follow-up: 42 months	Mean age: NR Gender:NR Nsmokers= 102 (history of stroke/TIA) Nsmokers=13/49 (26.5%; intervention) Nsmokers=14/53 (26.4%; control)	4	Nintervention = 1/13 (0.07%) Ncontrol=0/14 (0.00%)

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Table 1: Characteristics of included studies cntd.

Study identification	Type of SCI/Control	Patient Characteristics	Study Quality (Jadad score)	Cessation rate
Papadakis et al. 2011 [11]	SCI: Counselling and free of cost quit smoking medications (NRT, Bupropion, Varenicline) Control: Usual care + prescriptions to pharmacotherapy Follow-up: 26 weeks	Mean age:54.5±10.5 yrs. Gender:70% male Nsmokers= 28 (stroke and TIA)	4	Nintevention=4/15 (26.6%) Ncontrol= 2/13 (15.4%)
Frandsend et al. 2012 [12]	SCI: Counselling and cost-free NRT (gum, tablets, patches, nasal spray) Follow-up: 6 months	Mean age: 55.3 (SD not reported) Female: 41.5% Nsmokers=94 (stroke and TIA)	4	Nintervention= 16/49 (32.7%) Ncontrol=13/45 (28.9%)

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Key words: Smoking cessation, systematic review, stroke

Word count: 2927

Abstract

Objective: The main objective of this study was to determine the effectiveness of smoking cessation interventions for increasing cessation rates in smokers with cerebrovascular disease.

Design: Systematic review and meta-analyses. Two independent reviewers searched information sources and assessed studies for inclusion/exclusion criteria.

Eligibility criteria for included studies: Randomized control trials conducted prior to the 22nd of May 2012 investigating smoking cessation interventions in smokers with cerebrovascular disease were included. No age or ethnicity limitations were applied to be as inclusive as possible.

Methods: We followed the PRISMA statement approach to identify relevant randomized control studies. Due to the variability of interventions used in the reported studies, a meta-analysis was not conducted.

Results: Of 852 identified articles, 4 articles fit the inclusion criteria describing the outcome in 303 patients. The overall cessation rate with a smoking cessation intervention was 23.9% (42 out of 176) while without one was 20.8% (37 out of 178).

Conclusions: There is a limited number of reported intervention studies that explore this area of secondary stroke prevention. Furthermore, of those intervention studies that were found, only two implemented evidence based approaches to smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger studies with homogenous interventions are needed to determine how effective SCIs are in increasing cessation in smokers with established cerebrovascular disease.

ARTICLE SUMMARY

Article focus

- To explore the effectiveness of smoking cessation interventions in smokers with cerebrovascular disease.

Key messages

- There are a limited number of intervention studies that explore this area of stroke prevention.
- Of those intervention studies found, only a handful employed evidence based approaches to smoking cessation.
- A meta-analysis was not conducted due to the variability of reported intervention studies.

Strengths and limitations of this study

- This is the first review to explore the effectiveness of stop smoking interventions in this high risk group of smokers.
- This review explores the breadth of potential smoking cessation interventions in stroke and TIA patients.
- Limitations of this study include a small number of available of studies, large variability in population, intervention and outcome.

Introduction

Smoking prevalence has decreased in the United States over the last 40 years and as of 2009, approximately 46 million people, or 20.6% of all adults (aged 18 years and older), in the United States smoked cigarettes.[1] It is estimated that over a quarter of all strokes can be attributed to smoking.[2] Large epidemiological cohort studies have demonstrated that cigarette smoking is a major independent risk factor for ischemic stroke.[3, 4, 5]

The Framingham Heart Study demonstrated that heavy smokers (>40 cigarettes/day) were twice as likely to have a stroke compared to light smokers (between 1 and 10 cigarettes).[3] The risk of stroke decreased after two years of smoking cessation and was at the level of a non-smoker after five years of quitting.[3]

A meta-analysis of thirty-two studies found an increase of 50% relative risk [RR] of strokes (95% confidence interval [CI] 1.4 to1.6) was associated with cigarette smoking.[4] These studies provide support to the benefits of smoking cessation in patients with cerebrovascular disease. The risk of stroke declines soon after cessation among smokers regardless of age.[5]The data from observational studies have led to the general acceptance of the benefit of smoking cessation in stroke prevention. There is a lack of interventional studies and what is less established is the relative benefit of smoking cessation interventions (SCIs) in the stroke population.

The purpose of this systematic review is to present up-to-date information regarding the effectiveness of SCIs for increasing cessation rates in patients with established cerebrovascular disease.

Methods

Data sources

Studies were identified from MEDLINE (1980 to Present), EMBASE (1980 to Present) and CENTRAL (May 22, 2012) databases.The following MeSH terms were used to search the MEDLINE database: "smoking cessation", "stop or quit or cease or cessation", "cerebrovascular disorders", " brain ischemia","transient ischemic attack", "brain or cerebral", "brain hemorrhage", "brain or intracranial","cerebrum or cerebral", "stroke", " brain embolism and occlusive cerebrovascular disease". Similar terms were used for EMBASE and CENTRAL databases.

Study selection

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[6]for randomized control trials. We included studies if: 1) patients were diagnosed with cerebrovascular disease by a physician or neurologist. 2) We applied no ethnicity or age limitations in order to be as inclusive as possible. 3) We also included studies that reported smoking cessation intervention conditions (behavioural, pharmacotherapy, combination therapy).Finally, we excluded studies that did not report cessation rates.

Data extraction

We used a standardized form completed by two reviewers independently. We resolved discrepancies by consensus. Extracted data consisted of study characteristics (first author, year publication), patient characteristics (mean age, number of smokers, type of stroke diagnosis), type of SCI (behavioural, pharmacotherapy, combination), length of follow-up of the intervention and cessation rates.

Outcome of interest

The main outcome of interest was the number of patients who quit smoking either using a smoking cessation intervention versus those who did not. Cessation rates were used from follow-up data from each study. Lost to follow-up patients were included in the denominators and were considered as smokers.

Quality of assessment of primary studies

We appraised selected articles for their methodological quality and bias using the Jadad scale.[7]The Jadad scale takes into account several methodological characteristics of clinical studies such as blinding, randomization and dropouts.[7]Scores less than 3 were considered as low quality.

Results

Effect of SCI on long-term quit rates

Of 852 articles identified, 4 articles were deemed to fit the inclusion criteria. Characteristics and flow of included studies can be found in Table 1 and Figure 1 respectively. An overall Jadad score of the selected papers was 3.75 out of a possible score of 5. With an intervention, 42 out of 176 smokers quit versus 37 out of 178 in the control group. This resulted in an overall cessation rate of 23.9% for the intervention group compared to 20.8% for the control group.

Results of individual studies and risk of bias across studies

The first study explored the role of a patient and general practitioner systematic follow-up intervention to improve risk factor management after stroke.[8]The study recruited 523 consecutive incident stroke survivors of which 154 (29.4%) patients were identified as smokers at baseline. They were then randomized into the control (n=78) and intervention group (n=76).

The overall intervention involved providing tailored evidence-based management advice to general practitioners, patients, and caregivers post-stroke. The advice consisted of treatment with antihypertensive therapy, treatment with antiplatelet therapy, and smoking cessation. Smoking cessation advice was provided in regards to nicotine replacement therapy (NRT) use .[8]The authors found that at 1 year, 21 out of 76 (27.6%) patients in the intervention group who received smoking cessation advice in regards to NRT quit smoking. In the control group at 1 year, 22 out of 78 (28.2%) patients successfully quit smoking.[8]

The second study explored the impact of a stroke nurse specialist's input on risk factor modification.[9] The population was selected from a clinic of ambulant patients with a diagnosis of stroke or TIA who were attending for on-going rehabilitation in a UK teaching hospital. There were 205 patients recruited, of which 78 patients were identified as smokers (38.0%). The intervention consisted of meetings at 3 month intervals with a stroke nurse specialist to discuss modification of lifestyle (diet, exercise or increased activity, smoking). The control group received usual care from medical staff.[9]Upon review of this paper, it was noted that cessation rates in the original paper were not reported. We consulted the principal investigator and cessation rates are reported here from a 3 year follow-up study from McManus and associates from the original cohort.[10]Reported cessation rates in the intervention group at 42 months was found to be 1 out of 36 (2.8%).[10]None had quit in the control group (0 out of 42, 0.0%).[10]

The third study was a pilot trial of standardized counseling and cost-free pharmacotherapy for smoking cessation in secondary stroke prevention.[11]Patients who have recently experienced a TIA or stroke or have been identified as being at high risk for a cerebrovascular event were recruited and were randomized to either cost-free (CF) intervention or prescription (P) control group. Patients randomized in the CF group received free of cost

medications along with counseling with a smoking cessation nurse for 26 weeks.[11] There were 255 smokers were identified and 28 participants were enrolled based on readiness to quit. The control group received usual care and prescriptions to pharmacotherapy. Cessation rates at 26 weeks for the intervention and control group was 4 out of 15 (26.6%) and 2 out of 13 (15.4%) respectively.[11]

The fourth study examined the difference between a minimal versus intensive smoking cessation intervention in increasing cessation rates in recruited patients with a recent stroke or TIA.[12] There were 94 smoking patients with a recent stroke or TIA that were recruited for this study.[12] For the purpose of this review, the intensive smoking cessation intervention was regarded as the intervention group as this would be above and beyond what would be available in a 'real world' setting. To simplify the comparison group and due to the accessibility of smoking cessation counseling through a primary care physician or even a smoker's helpline, the minimal smoking cessation intervention group was considered the 'control' group. The control group consisted of a 30 minute counseling session with the study nurse advising patients to quit smoking.[12] A total of 45 patients were randomized into the control group.[12] The intervention group received five sessions of smoking cessation counseling with the study nurse while receiving free NRT.[12]A total of 49 patients were randomized into the intervention group.[12]Cessation rates at 6 months for the intervention and control group was 16 out of 49 (32.7%) and 13 out of 45 (28.9%)respectively.[12]

There were some limitations to each study. Sample size was an issue in all of the included studies. For example the small number of participants (n =28) in Papadakis et al.'s study meant that the study was relatively underpowered.[11] Similarly, only 94 patients were recruited in the Frandsend et al.'s study. This study saw little effect of the intensive smoking

cessation intervention.[12] A larger trial would be needed to further explore the favourable trend documented in both studies. Furthermore, the provision of pharmacotherapy, counseling and follow-up may be an enhancement to 'real world' standard of care experienced by TIA and stroke patients. A similar underpowered result due to a small sample size was observed in the study by Ellis et al./McManus et al.[9,10] They noted that the risk factor control in the control group was better than anticipated from pilot studies and in comparison to other trial evidence. Finally, all included studies recruited patients from fairly homogenous sources such as 2 GP clinics,[8] hospitals[9, 12] and a single stroke clinic,[11] which may not be generalizable to a broader stroke population in other settings.

Discussion

The purpose of this systematic review was to determine the effectiveness of SCIs in increasing cessation rates in patients with established cerebrovascular disease.

Our results demonstrate that there were a limited number of reported interventional studies that explore this area of stroke prevention. Furthermore, there seems to be a lack of evidence based implementation of proven SCIs. There is a link between sub-optimal use of evidence based smoking cessation medications and pharmacotherapy to poorer rates of smoking abstinence.[11] We found that only two of the four interventional studies[11,12] implemented evidence based approaches to smoking cessation. The approach that these studies took fell in line with recommendations outlined in the *Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update.*[13]

Fiore and associates[13] suggested that effective smoking interventions consist of pharmacotherapy coupled with counseling and follow-up. First line pharmacotherapy such as

NRT, Buproprion and Varenicline can double or even triple the likelihood of long-term smoking abstinence for heavy smokers (who consume > 10 cigarettes per day) when coupled with behavioural counseling and follow-up.[14-16]

Smoking cessation interventions have been demonstrated to be effective in other populations in particular patients with coronary heart disease (CHD). CHD patients can benefit up to an increase of 44% in their cessation rate success.[17]A decrease of the risk of mortality and non-fatal myocardial infarction by 32% and 36% respectively has also been observed using this approach.[18] Larger clinical studies need to employ evidence based approaches to smoking cessation to determine their effectiveness in smokers with cerebrovascular disease.

There are several limitations in the present study, which should be considered in any interpretation of the findings. There was a high degree of variability in regards to the population, intervention and outcome. For example, an array of stroke diagnoses was found ranging from incident stroke and TIA. A meta-analysis was not conducted due to the varied interventions from the reported studies.. Wolfe and colleagues employed pharmacotherapy and advice on the use of these pharmacotherapies.[8] Ellis/McManus and associates[9, 10] used standard outpatient advice with post-discharge care from a nurse specialist. Papadakis and colleagues used cost-free pharmacotherapy with counseling support and follow-up. Finally, Frandsend et al.[11] used intensive counseling support with cost-free pharmacotherapy. Given these differences in interventions and that each study was set in different countries (United Kingdom, Canada and Denmark), would not have provided meaningful results from a meta-analysis. The duration of follow-up was also different amongst the included studies ranging from 3 to 42 months. Finally cessation was only quantified biochemically by only two studies.[11, 12] Wolfe and associates[8] used both biochemical assays along with self-reported smoking status to quantify cessation. However,

these authors only used the biochemical assays to determine the amount of misreporting in self-reported data and did not correct misreported smoking status.[8] Ellis and colleagues did not report how cessation was quantified.[9]

Conclusion

The paper provided results from a systematic review that explored the effectiveness of SCIs for increasing cessation rates. We found a limited number of reported studies that explored this area of secondary stroke prevention. Furthermore, of those interventional studies that were found, only two studies implemented evidence-based approaches in smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger studies with homogenous interventions are needed to determine how effective SCIs are in increasing cessation in smokers with established cerebrovascular disease.

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The Effectiveness of Smoking Cessation Interventions in Smokers with Cerebrovascular Disease: A systematic review.

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Abstract

Objective: The main objective of this study was to determine the effectiveness of smoking cessation interventions for increasing cessation rates in smokers with cerebrovascular disease.

Design: Systematic review and meta-analyses. Two independent reviewers searched information sources and assessed studies for inclusion/exclusion criteria.

Eligibility criteria for included studies: Randomized control trials conducted prior to the 22nd of May 2012 investigating smoking cessation interventions in smokers with cerebrovascular disease were included. No age or ethnicity limitations were applied to be as inclusive as possible.

Methods: We followed the PRISMA statement approach to identify relevant randomized control studies. Due to the variability of interventions used in the reported studies, a meta-analysis was not conducted. ~~We used a mixed effects Mantel-Haenszel approach meta-analysis to pool estimate effects for randomized control trials.~~

Results: Of 852 identified articles, 4 articles fit the inclusion criteria describing the outcome in 303 patients. The overall cessation rate with a smoking cessation intervention was 238.91% (42 out of 17653) while without one was 20.84.7% (37 out of 17850). ~~However, the meta-analysis revealed a non-significant effect of using a smoking cessation intervention on quitting (RR 1.19; 95% CI 0.81 to 1.73; p=0.38, I^2=0.00).~~

Conclusions: There is a limited number of reported intervention studies that explore this area of secondary stroke prevention. Furthermore, of those intervention studies that were found, only two implemented evidence based approaches to smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger studies with homogenous interventions are needed to determine how effective SCIs are in increasing

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cessation in smokers with established cerebrovascular disease.~~More studies are needed to determine how effective SCI's are for increasing cessation rates in this high risk population of smokers.~~

ARTICLE SUMMARY

Article focus

- To explore the effectiveness of smoking cessation interventions in smokers with cerebrovascular disease.

Key messages

- There are a limited number of intervention studies that explore this area of stroke prevention.
- Of those intervention studies found, only a handful employed evidence based approaches to smoking cessation.
- A meta-analysis was not conducted due to the variability of reported intervention studies.

Strengths and limitations of this study

- This is the first review to explore the effectiveness of stop smoking interventions in this high risk group of smokers.
- This review explores the breadth of potential smoking cessation interventions in stroke and TIA patients.
- Limitations of this study include a small number of available of studies, large variability in population, intervention and outcome.

Introduction

Smoking prevalence has decreased in the United States over the last 40 years and as of 2009, approximately 46 million people, or 20.6% of all adults (aged 18 years and older), in the United States smoked cigarettes.[1] It is estimated that over a quarter of all strokes can be attributed to smoking.[2] Large epidemiological cohort studies have demonstrated that cigarette smoking is a major independent risk factor for ischemic stroke.[3, 4, 5]

The Framingham Heart Study demonstrated that heavy smokers (>40 cigarettes/day) were twice as likely to have a stroke compared to light smokers (between 1 and 10 cigarettes~~< 10 cigarettes/day~~).[3] The risk of stroke decreased after two years of smoking cessation and was at the level of a non-smoker after five years of quitting.[3]

A meta-analysis of thirty-two studies found an increase of 50% relative risk [RR] of strokes (95% confidence interval [CI] 1.4 to1.6) was associated with cigarette smoking.[4] These studies provide support to the benefits of smoking cessation in patients with cerebrovascular disease. The risk of stroke declines soon after cessation among smokers regardless of age.[5]The data from observational studies have led to the general acceptance of the benefit of smoking cessation in stroke prevention. There is a lack of interventional studies and what is less

established is the relative benefit of smoking cessation interventions (SCI's) in the stroke population.

The purpose of this systematic review is to present up-to-date information regarding the effectiveness of SCIs for increasing cessation rates in patients with established cerebrovascular disease.

Methods

Data sources

Studies were identified from MEDLINE (1980 to Present), EMBASE (1980 to Present) and CENTRAL (May 22, 2012) databases.The following MeSH terms were used to search the MEDLINE database: "smoking cessation", "stop or quit or cease or cessation", "cerebrovascular disorders", " brain ischemia","transient ischemic attack", "brain or cerebral", "brain hemorrhage", "brain or intracranial","cerebrum or cerebral", "stroke", " brain embolism and occlusive cerebrovascular disease". Similar terms were used for EMBASE and CENTRAL databases.

Study selection

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[6]for randomized control trials. We included studies if: 1) patients were diagnosed with cerebrovascular disease by a physician or neurologist. 2) We applied no ethnicity or age limitations in order to be as inclusive as possible. 3) We also included studies that reported smoking cessation intervention conditions (behavioural, pharmacotherapy, combination therapy). 4)Finally, we excluded studies that did not report cessation rates.

Data extraction

We used a standardized form completed by two reviewers independently. We resolved discrepancies by consensus. Extracted data consisted of study characteristics (first author, year publication), patient characteristics (mean age, number of smokers, type of stroke diagnosis), type of SCI (behavioural, pharmacotherapy, combination), ~~length~~ length of follow-up of the intervention and cessation rates.

Outcome of interest

The main outcome of interest was the number of patients who quit smoking either using a smoking cessation intervention versus those who did not. Cessation rates were used from follow-up data from each study. Lost to follow-up patients were included in the denominators and were considered as smokers.

Quality of assessment of primary studies

We appraised selected articles for their methodological quality and bias using the Jadad scale.[7] The Jadad scale takes into account several methodological characteristics of clinical studies such as blinding, randomization and dropouts.[7] Scores less than 3 were considered as low quality.

~~**Statistical Analysis**~~

~~We used a mixed model Mantel-Haenszel meta-analysis approach to combine pooled effect estimates and 95% CI's were calculated. The I^2 test was used to determine whether there was statistical heterogeneity between individual studies. Comprehensive meta-analysis 2.0 statistical software was used for the analyses.~~

Results

Effect of SCI on long-term quit rates

Of 852 articles identified, 4 articles were deemed to fit the inclusion criteria. Characteristics and flow of included studies can be found in Table 1 and Figure 1 respectively. ~~The mean age of smokers was 66.5 (+/- 12.5).~~ An overall Jadad score of the selected papers was 3.75 out of a possible score of 5. With an intervention, 42 out of 176~~153~~ smokers quit versus 37 out of 178~~50~~ in the control group. This resulted in an overall cessation rate of 23.9~~28.1~~% for the intervention group compared to 20.8~~4.7~~% for the control group. ~~The meta-analysis revealed a non-significant effect of using a SCI on quitting (RR 1.19; 95% CI 0.81 to 1.73; p=0.38, I^2=0.00) (Figure 2).~~

Results of individual studies and risk of bias across studies

The first study explored the role of a patient and general practitioner systematic follow-up intervention to improve risk factor management after stroke.[8] The study recruited 523 consecutive incident stroke survivors of which 154 (29.4%) patients were identified as smokers at baseline. They were then randomized into the control (n=78) and intervention group (n=76). The overall intervention involved providing tailored evidence-based management advice to general practitioners, patients, and caregivers post-stroke. The advice consisted of treatment with antihypertensive therapy, treatment with antiplatelet therapy, and smoking cessation. Smoking cessation advice was provided in regards to nicotine replacement therapy (NRT) use .[8] The authors found that at 1 year, 21 out of ~~/~~76 (27.6%) patients in the intervention group who received smoking cessation advice in regards to NRT quit smoking. In the control group at 1 year, 22 out of ~~/~~78 (28.2%) patients successfully quit smoking.[8]

The second study explored the impact of a stroke nurse specialist's input on risk factor modification.[9] The population was selected from a clinic of ambulant patients with a diagnosis of stroke or TIA who were attending for on-going rehabilitation in a UK teaching hospital. There were 205 patients recruited, of which 78 patients were identified as smokers (38.0%). ~~There were 36/100 (36%) patients thatwere randomized into the intervention group and 42/105 (40%) were randomized into the control group.~~ The intervention consisted of meetings at 3 month intervals with a stroke nurse specialist to discuss modification of lifestyle (diet, exercise or increased activity, smoking). The control group received usual care from medical staff.[9]Upon review of this paper, it was noted that cessation rates in the original paper were not reported. We consulted the principal investigator and cessation rates are reported here from a 3 year follow-up study from McManus and associates from the original cohort.[10]Reported cessation rates in the intervention group at 42 months was found to be 1 out of ~~/36~~13 (~~7~~2.8~~0.07~~%).[10]None had quit in the control group (0 out of ~~/42, 0.0%~~14).[10]

The third study was a pilot trial of standardized counseling and cost-free pharmacotherapy for smoking cessation in secondary stroke prevention.[11]Patients who have recently experienced a TIA or stroke or have been identified as being at high risk for a cerebrovascular event were recruited and were randomized to either cost-free (CF) intervention or prescription (P) control group. Patients randomized in the CF group received free of cost medications along with counseling with a smoking cessation nurse for 26 weeks.[11] There were 255 smokers were identified and 28 participants were enrolled based on readiness to quit. The control group received usual care and prescriptions to pharmacotherapy. Cessation rates at 26 weeks for the intervention and control group was 4 out of ~~/~~15 (26.6%) and 2 out of ~~/~~13 (15.4%) respectively.[11]

The fourth study examined the difference between a minimal versus intensive smoking cessation intervention in increasing cessation rates in recruited patients with a recent stroke or TIA.[12] There were 94 smoking patients with a recent stroke or TIA that were recruited for this study.[12] For the purpose of this review, ~~and meta-analysis,~~ the ~~the minimal smoking cessation intervention was considered as the control group while the~~ intensive smoking cessation intervention was regarded as the intervention group ~~-~~ as this would be above and beyond what would be available in a 'real world' setting. To simplify the comparison group and due to the accessibility of smoking cessation counseling through a primary care physician or even a smoker's helpline, the minimal smoking cessation intervention group was considered the 'control' group. The control group consisted of a 30 minute counseling session with the study nurse advising patients to quit smoking.[12] A total of 45 patients were randomized into the control group.[12] The intervention group received five sessions of smoking cessation counseling with the study nurse while receiving free NRT.[12] A total of 49 patients were randomized into the intervention group.[12] Cessation rates at 6 months for the intervention and control group was 16 out of ~~/~~49 (32.7%) and 13 out of ~~/~~45 (28.9%) ~~and16/49 (32.7%)~~ respectively.[12]

~~The methodological quality of each study scored collectively 3.75 out of 5 on the Jadad scale.~~ There were some limitations to each study. Sample size was an issue in all of the included studies. For example the small number of participants (n =28) in Papadakis et al.'s study meant that the study was relatively underpowered.[11] Similarly, only ~~a limited~~ 94 ~~number of~~ patients were ~~(*n*=94)~~ recruited in the Frandsend et al.'s study. This study saw little effect of the intensive smoking cessation intervention.[12] A larger trial would be needed to further explore the favourable trend documented in both studies. Furthermore, the provision of pharmacotherapy, counseling and follow-up may be an enhancement to 'real world' standard of care experienced by TIA and

stroke patients. A similar underpowered result due to a small sample size was observed in the study by Ellis et al./McManus et al.[9,10] They noted that the risk factor control in the control group was better than anticipated from pilot studies and in comparison to other trial evidence. Finally, all included studies recruited patients from fairly homogenous sources such as 2 GP clinics,[8] hospitals[9,12] and a single stroke clinic,[11] which may not be generalizable to a broader stroke population in other settings.

Discussion

The purpose of this systematic review was to determine the effectiveness of SCIs in increasing cessation rates in patients with established cerebrovascular disease.

Our results demonstrate that there ~~was~~were a limited number of reported interventional studies that explore this area of stroke prevention. ~~which may have contributed to the lack of statistical significance in our meta-analyses.~~ Furthermore, there seems to be a lack of evidence based implementation of proven SCIs. There is a link between sub-optimal use of evidence based smoking cessation medications and pharmacotherapy to poorer rates of smoking abstinence.[11] We found that only two of the four interventional studies[11,12] implemented evidence based approaches to smoking cessation. The approach that these studies took fell in line with recommendations outlined in the *Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update.*[13]

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Smoking cessation interventions have been demonstrated to be effective in other populations in particular patients with coronary heart disease (CHD). CHD patients can benefit up to an increase of 44% in their cessation rate success.[17]A decrease of the risk of mortality and non-fatal myocardial infarction by 32% and 36% respectively has also been observed using this approach.[18] Larger clinical studies need to employ evidence based approaches to smoking cessation to determine their effectiveness in smokers with cerebrovascular disease.

There are several limitations in the present study, which should be considered in any interpretation of the findings. There was a high degree of variability in~~heterogeneity among pooled data for the meta-analysis in regards t~~ regards to~~o~~ the population, intervention and outcome. ~~There was significant variability in the population of the included studies.~~ For example, an array of stroke diagnoses was found ranging from incident stroke and TIA. A meta-analysis was not conducted due to the varied ~~Pooled~~ interventions from the reported~~also varied between~~ studies. ~~p~~. Wolfe and colleagues employed pharmacotherapy and advice on the use of these pharmacotherapies ~~(8),~~[8] Ellis/McManus and associates[9, 10] used standard outpatient advice with post-discharge care from a nurse specialist. Papadakis and colleagues used cost-free pharmacotherapy with counseling support and follow-up. Finally, Frandsend et al.[11] ~~,~~ used intensive counseling support with cost-free pharmacotherapy. Given these differences in interventions and that each study was set in different countries (United Kingdom, Canada and Denmark), would not have provided meaningful results from a meta-analysis. The duration of follow-up was also different amongst the included studies ranging from 3 to 42 months. Finally cessation was only quantified biochemically by only two studies.[11, 12] Wolfe and associates[8] used

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Conclusion

The paper provided results from a systematic review that explored the effectiveness of SCI's for increasing cessation rates. We found a limited number of reported studies that explored this area of secondary stroke prevention. Furthermore, of those interventional studies that were found, only two studies implemented evidence-based approaches in smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger studies with ~~uniform~~homogenous interventions are needed to determine how effective SCI's are in increasing cessation in smokers with established cerebrovascular disease.

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Table 1: Characteristics of included studies

Study identification	Type of SCI/Control	Patient Characteristics	Jadad score	Cessation rate
Wolfe et al. [8]	SCI: Advice on NRT use Control: Usual care Follow-up: 1 year	Intervention: 61 (22.3%) over 80 years, 126 (46.2%) female, 76 (27.9%) smokers. Control: 50 (20.2%) over 80 years, 118 (47.8%) female, 78 (32.2%) smokers.	3	Nintervention=21 out of 76 (27.6%) Ncontrol=22 out of 78 (28.2%)
Ellis et al.[9]/McManus et al.[10]	SCI: Discussion with nurse specialist on lifestyle modification in regards to smoking cessation Control: Usual care Follow-up: 42 months	Intervention: 64.3 (62.4-66.1, SD) mean age, 54 (54%.0) male, 36 (36.0%) smokers. Control: 65.8 (64.0-67.5), 52 (50.0%) male, 40 (40.0%) smokers.	4	Nintervention =1 out of 36 (2.8%) Ncontrol=0 out of 42 (0.0%)

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Table 1: Characteristics of included studies cntd.

Study identification	Type of SCI/Control	Patient Characteristics	Study Quality (Jadad score)	Cessation rate
Papadakis et al.[11]	SCI: Counseling and cost free quit smoking medications (NRT, Bupropion, Varenicline) with follow-up Control: Usual care + prescriptions to pharmacotherapy Follow-up: 26 weeks	Intervention: 55.4 (12.4 SD) mean age, 53.3% male, 15 (53.6%) smokers. Control: 53.5 (8.1 SD), mean age, 69.2% male, 13 (46.4%) smokers.	4	Nintevention=4 out of 15 (26.6%) Ncontrol=2 out of 13 (15.4%)
Frandsend et al.[12]	SCI: Counseling and cost-free NRT (gum, tablets, patches, nasal spray) with follow-up Control: 1 time 30 min counseling support Follow-up: 6 months	Intervention: 29 (59.2%) age 50-65, 17 (34.7%) female, 49 smokers. Control: 21 (46.7%) 50-65 age, 22 (48.9%) female, 45 smokers.	4	Nintervention=16 out of 49 (32.7%) Ncontrol=13 out of 45 (28.9%)

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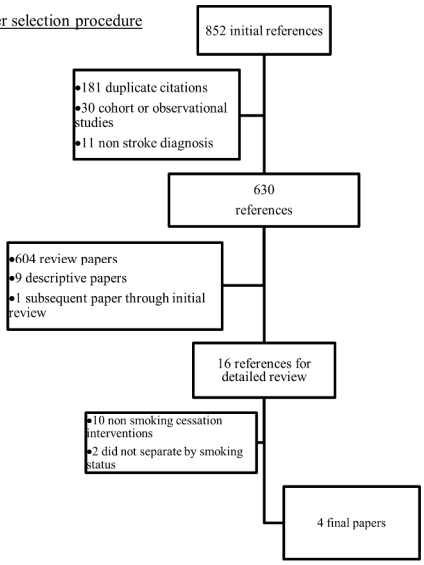
Figure 1: Exclusion criteria and paper selection procedure



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The Effectiveness of Smoking Cessation Interventions in Smokers with Cerebrovascular Disease: A systematic review.

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The Effectiveness of Smoking Cessation Interventions in Smokers with Cerebrovascular Disease: A systematic review.

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Key words: Smoking cessation, systematic review, stroke

Word count: 2932

Abstract

Objective: The main objective of this study was to determine the effectiveness of smoking cessation interventions (SCIs) for increasing cessation rates in smokers with cerebrovascular disease.

Design: Systematic review. Two independent reviewers searched information sources and assessed studies for inclusion/exclusion criteria.

Eligibility criteria for included studies: Randomized control trials conducted prior to the 22nd of May 2012 investigating smoking cessation interventions in smokers with cerebrovascular disease were included. No age or ethnicity limitations were applied to be as inclusive as possible.

Methods: We followed the PRISMA statement approach to identify relevant randomized control studies. Due to the variability of interventions used in the reported studies, a meta-analysis was not conducted.

Results: Of 852 identified articles, 4 articles fit the inclusion criteria describing the outcome in 354 patients. The overall cessation rate with a smoking cessation intervention was 23.9% (42 out of 176) while without one was 20.8% (37 out of 178).

Conclusions: There is a limited number of reported intervention studies that explore this area of secondary stroke prevention. Furthermore, of those intervention studies that were found, only two-implemented evidence based approaches to smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger studies with homogenous interventions are needed to determine how effective SCIs are in increasing cessation in smokers with established cerebrovascular disease.

ARTICLE SUMMARY

Article focus

- To explore the effectiveness of smoking cessation interventions in smokers with cerebrovascular disease.

Key messages

- There are a limited number of intervention studies that explore this area of stroke prevention.
- Of those intervention studies found, only a handful employed evidence based approaches to smoking cessation.
- A meta-analysis was not conducted due to the variability of reported intervention studies.

Strengths and limitations of this study

- This is the first review to explore the effectiveness of stop smoking interventions in this high risk group of smokers.
- This review explores the breadth of potential smoking cessation interventions in stroke and transient ischemic attack (TIA) patients.
- Limitations of this study include a small number of available of studies, large variability in population, intervention and outcome.

Introduction

Smoking prevalence has decreased in the United States over the last 40 years and as of 2009, approximately 46 million people, or 20.6% of all adults (aged 18 years and older), in the United States smoked cigarettes.[1] It is estimated that over a quarter of all strokes can be attributed to smoking.[2] Large epidemiological cohort studies have demonstrated that cigarette smoking is a major independent risk factor for ischemic stroke.[3, 4, 5]

The Framingham Heart Study demonstrated that heavy smokers (>40 cigarettes/day) were twice as likely to have a stroke compared to light smokers (between 1 and 10 cigarettes).[3] The risk of stroke decreased after two years of smoking cessation and was at the level of a non-smoker after five years of quitting.[3]

A meta-analysis of thirty-two studies found an increase of 50% relative risk [RR] of strokes (95% confidence interval [CI] 1.4 to 1.6) was associated with cigarette smoking.[4] These studies provide support to the benefits of smoking cessation in patients with cerebrovascular disease. The risk of stroke declines soon after cessation among smokers regardless of age.[5]The data from observational studies have led to the general acceptance of the benefit of smoking cessation in stroke prevention. There is a lack of interventional studies and what is less established is the relative benefit of smoking cessation interventions (SCIs) in the stroke population.

The purpose of this systematic review is to present up-to-date information regarding the effectiveness of SCIs for increasing cessation rates in patients with established cerebrovascular disease.

Methods

Data sources

Studies were identified from MEDLINE (1980 to Present), EMBASE (1980 to Present) and CENTRAL (May 22, 2012) databases. The following MeSH terms were used to search the MEDLINE database: "smoking cessation", "stop or quit or cease or cessation", "cerebrovascular disorders", " brain ischemia","transient ischemic attack", "brain or cerebral", "brain hemorrhage", "brain or intracranial","cerebrum or cerebral", "stroke", " brain embolism and occlusive cerebrovascular disease". Similar terms were used for EMBASE and CENTRAL databases.

Study selection

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[6]for randomized control trials. We included studies if: 1) patients were diagnosed with cerebrovascular disease by a physician or neurologist. 2) we applied no ethnicity or age limitations in order to be as inclusive as possible. 3) we also included studies that reported smoking cessation intervention conditions (behavioural, pharmacotherapy, combination therapy). Finally, we excluded studies that did not report cessation rates.

Data extraction

We used a standardized form completed by two reviewers independently. We resolved discrepancies by consensus. Extracted data consisted of study characteristics (first author, year publication), patient characteristics (mean age, number of smokers, type of stroke diagnosis), type of SCI (behavioural, pharmacotherapy, combination), length of follow-up of the intervention and cessation rates.

Outcome of interest

The main outcome of interest was the number of patients who quit smoking either using a smoking cessation intervention versus those who did not. Cessation rates were used from follow-up data from each study. Lost to follow-up patients were included in the denominators and were considered as smokers.

Quality of assessment of primary studies

We appraised selected articles for their methodological quality and bias using the Jadad scale.[7]The Jadad scale takes into account several methodological characteristics of clinical studies such as blinding, randomization and dropouts.[7]Scores less than 3 were considered as low quality.

Results

Effect of SCI on long-term quit rates

Of 852 articles identified, 4 articles were deemed to fit the inclusion criteria. Characteristics and flow of included studies can be found in Table 1 and Figure 1 respectively. An overall Jadad score of the selected papers was 3.75 out of a possible score of 5. With an intervention, 42 out of 176 smokers quit versus 37 out of 178 in the control group. This resulted in an overall cessation rate of 23.9% for the intervention group compared to 20.8% for the control group.

Results of individual studies and risk of bias across studies

The first study explored the role of a patient and general practitioner systematic follow-up intervention to improve risk factor management after stroke.[8]The study recruited 523 consecutive incident stroke survivors of which 154 (29.4%) patients were identified as smokers

at baseline. They were then randomized into the control (n=78) and intervention group (n=76). The overall intervention involved providing tailored evidence-based management advice to general practitioners, patients, and caregivers post-stroke. The advice consisted of treatment with antihypertensive therapy, treatment with antiplatelet therapy, and smoking cessation. Smoking cessation advice was provided in regards to nicotine replacement therapy (NRT) use .[8]The authors found that at 1 year, 21 out of 76 (27.6%) patients in the intervention group who received smoking cessation advice in regards to NRT quit smoking. In the control group at 1 year, 22 out of 78 (28.2%) patients successfully quit smoking.[8]

The second study explored the impact of a stroke nurse specialist's input on risk factor modification.[9] The population was selected from a clinic of ambulant patients with a diagnosis of stroke or TIA who were attending for on-going rehabilitation in a UK teaching hospital. There were 205 patients recruited, of which 78 patients were identified as smokers (38.0%). The intervention consisted of meetings at 3 month intervals with a stroke nurse specialist to discuss modification of lifestyle (diet, exercise or increased activity, smoking). The control group received usual care from medical staff.[9]Upon review of this paper, it was noted that cessation rates in the original paper were not reported. We consulted the principal investigator and cessation rates are reported here from a 3 year follow-up study from McManus and associates from the original cohort.[10]Reported cessation rates in the intervention group at 42 months was found to be 1 out of 36 (2.8%).[10]None had quit in the control group (0 out of 42, 0.0%).[10]

The third study was a pilot trial of standardized counseling and cost-free pharmacotherapy for smoking cessation in secondary stroke prevention.[11]Patients who have recently experienced a TIA or stroke or have been identified as being at high risk for a cerebrovascular event were recruited and were randomized to either cost-free (CF) intervention

or prescription (P) control group. Patients randomized in the CF group received free of cost medications along with counseling with a smoking cessation nurse for 26 weeks.[11] There were 255 smokers were identified and 28 participants were enrolled based on readiness to quit. The control group received usual care and prescriptions to pharmacotherapy. Cessation rates at 26 weeks for the intervention and control group was 4 out of 15 (26.6%) and 2 out of 13 (15.4%) respectively.[11]

The fourth study examined the difference between a minimal versus intensive smoking cessation intervention in increasing cessation rates in recruited patients with a recent stroke or TIA.[12] There were 94 smoking patients with a recent stroke or TIA that were recruited for this study.[12] For the purpose of this review, the intensive smoking cessation intervention was regarded as the intervention group as this would be above and beyond what would be available in a 'real world' setting. To simplify the comparison group and due to the accessibility of smoking cessation counseling through a primary care physician or even a smoker's helpline, the minimal smoking cessation intervention group was considered the 'control' group. The control group consisted of a 30 minute counseling session with the study nurse advising patients to quit smoking.[12] A total of 45 patients were randomized into the control group.[12] The intervention group received five sessions of smoking cessation counseling with the study nurse while receiving free NRT.[12] A total of 49 patients were randomized into the intervention group.[12] Cessation rates at 6 months for the intervention and control group was 16 out of 49 (32.7%) and 13 out of 45 (28.9%) respectively.[12]

There were some limitations to each study. Sample size was an issue in all of the included studies. For example the small number of participants (n=28) in Papadakis et al.'s study meant that the study was relatively underpowered.[11] Similarly, only 94 patients were

recruited in the Frandsend et al.'s study. This study saw little effect of the intensive smoking cessation intervention.[12]A larger trial would be needed to further explore the favourable trend documented in both studies. Furthermore, the provision of pharmacotherapy, counseling and follow-up may be an enhancement to 'real world' standard of care experienced by TIA and stroke patients. A similar underpowered result due to a small sample size was observed in the study by Ellis et al./McManus et al.[9,10] They noted that the risk factor control in the control group was better than anticipated from pilot studies and in comparison to other trial evidence. Finally, all included studies recruited patients from fairly homogenous sources such as 2 GP clinics,[8] hospitals[9, 12] and a single stroke clinic,[11] which may not be generalizable to a broader stroke population in other settings.

Discussion

The purpose of this systematic review was to determine the effectiveness of SCIs in increasing cessation rates in patients with established cerebrovascular disease.

Our results demonstrate that there were a limited number of reported interventional studies that explore this area of stroke prevention. Furthermore, there seems to be a lack of evidence-based implementation of proven SCIs. There is a link between sub-optimal use of evidence-based smoking cessation medications and pharmacotherapy to poorer rates of smoking abstinence.[11] We found that only two of the four interventional studies[11,12] implemented evidence based approaches to smoking cessation. The approach that these studies took fell in line with recommendations outlined in the *Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update.*[13]

Fiore and associates[13]suggested that effective smoking interventions consist of pharmacotherapy coupled with counseling and follow-up. First line pharmacotherapy such as NRT, Buproprion and Varenicline can double or even triple the likelihood of long-term smoking abstinence for heavy smokers (who consume > 10 cigarettes per day) when coupled with behavioural counseling and follow-up.[14-16]

Smoking cessation interventions have been demonstrated to be effective in other populations in particular patients with coronary heart disease (CHD). CHD patients can benefit up to an increase of 44% in their cessation rate success.[17]A decrease of the risk of mortality and non-fatal myocardial infarction by 32% and 36% respectively has also been observed using this approach.[18] Larger clinical studies need to employ evidence based approaches to smoking cessation to determine their effectiveness in smokers with cerebrovascular disease.

There are several limitations in the present study, which should be considered in any interpretation of the findings. There was a high degree of variability in regards to the population, intervention and outcome. For example, an array of stroke diagnoses was found ranging from incident stroke and TIA. A meta-analysis was not conducted due to the varied interventions from the reported studies.. Wolfe and colleagues employed pharmacotherapy and advice on the use of these pharmacotherapies.[8] Ellis/McManus and associates[9, 10] used standard outpatient advice with post-discharge care from a nurse specialist. Papadakis and colleagues used cost-free pharmacotherapy with counseling support and follow-up. Finally, Frandsend et al.[11] used intensive counseling support with cost-free pharmacotherapy. Given these differences in interventions and that each study was set in different countries (United Kingdom, Canada and Denmark), would not have provided meaningful results from a meta-analysis. The duration of follow-up was also different amongst the included studies ranging from 3 to 42 months. Finally,

cessation was only quantified biochemically by only two studies.[11, 12] Wolfe and associates[8] used both biochemical assays along with self-reported smoking status to quantify cessation. However, these authors only used the biochemical assays to determine the amount of misreporting in self-reported data and did not correct misreported smoking status.[8] Ellis and colleagues did not report how cessation was quantified.[9]

Conclusion

The paper provided results from a systematic review that explored the effectiveness of SCIs for increasing cessation rates. We found a limited number of reported studies that explored this area of secondary stroke prevention. Furthermore, of those interventional studies that were found, only two studies implemented evidence-based approaches in smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger studies with homogenous interventions are needed to determine how effective SCIs are in increasing cessation in smokers with established cerebrovascular disease.

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Funding: None delcared

Contributorship statement: R. Edjoc performed primary drafting of the manuscript along with data extraction and analyses. R. Reid formulated the research question and provided feedback on the manuscript. M. Sharma provided feedback on the drafted manuscript. N. Bresee aided in the extraction process of data from gathered papers.

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Key words: Smoking cessation, systematic review, stroke

Word count: ~~29272~~2932

Abstract

Objective: The main objective of this study was to determine the effectiveness of smoking cessation interventions (SCIs) for increasing cessation rates in smokers with cerebrovascular disease.

Design: Systematic review ~~and meta-analyses~~. Two independent reviewers searched information sources and assessed studies for inclusion/exclusion criteria.

Eligibility criteria for included studies: Randomized control trials conducted prior to the 22nd of May 2012 investigating smoking cessation interventions in smokers with cerebrovascular disease were included. No age or ethnicity limitations were applied to be as inclusive as possible.

Methods: We followed the PRISMA statement approach to identify relevant randomized control studies. Due to the variability of interventions used in the reported studies, a meta-analysis was not conducted. ~~We used a mixed effects Mantel-Haenszel approach meta-analysis to pool estimate effects for randomized control trials.~~

Results: Of 852 identified articles, 4 articles fit the inclusion criteria describing the outcome in ~~303~~ 354 patients. The overall cessation rate with a smoking cessation intervention was 2~~3~~8.9~~1~~% (42 out of 176~~53~~) while without one was 20.8~~4.7~~% (37 out of 178~~50~~). ~~However, the meta-analysis revealed a non-significant effect of using a smoking cessation intervention on quitting (RR 1.19; 95% CI 0.81 to 1.73; p=0.38, I^2=0.00).~~

Conclusions: There is a limited number of reported intervention studies that explore this area of secondary stroke prevention. Furthermore, of those intervention studies that were found, only ~~two implemented~~two-implemented evidence based approaches to smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger

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studies with homogenous interventions are needed to determine how effective SCIs are in increasing cessation in smokers with established cerebrovascular disease. ~~More studies are needed to determine how effective SCI's are for increasing cessation rates in this high risk population of smokers.~~

ARTICLE SUMMARY

Article focus

- To explore the effectiveness of smoking cessation interventions in smokers with cerebrovascular disease.

Key messages

- There are a limited number of intervention studies that explore this area of stroke prevention.
- Of those intervention studies found, only a handful employed evidence based approaches to smoking cessation.
- A meta-analysis was not conducted due to the variability of reported intervention studies.

Strengths and limitations of this study

- This is the first review to explore the effectiveness of stop smoking interventions in this high risk group of smokers.
- This review explores the breadth of potential smoking cessation interventions in stroke and transient ischemic attack (TIA) patients.
- Limitations of this study include a small number of available of studies, large variability in population, intervention and outcome.

Introduction

Smoking prevalence has decreased in the United States over the last 40 years and as of 2009, approximately 46 million people, or 20.6% of all adults (aged 18 years and older), in the United States smoked cigarettes.[1] It is estimated that over a quarter of all strokes can be attributed to smoking.[2] Large epidemiological cohort studies have demonstrated that cigarette smoking is a major independent risk factor for ischemic stroke.[3, 4, 5]

The Framingham Heart Study demonstrated that heavy smokers (>40 cigarettes/day) were twice as likely to have a stroke compared to light smokers (between 1 and 10 cigarettes~~< 10 cigarettes/day~~).[3] The risk of stroke decreased after two years of smoking cessation and was at the level of a non-smoker after five years of quitting.[3]

A meta-analysis of thirty-two studies found an increase of 50% relative risk [RR] of strokes (95% confidence interval [CI] 1.4 to 1.6) was associated with cigarette smoking.[4] These studies provide support to the benefits of smoking cessation in patients with cerebrovascular disease. The risk of stroke declines soon after cessation among smokers regardless of age.[5]The data from observational studies have led to the general acceptance of the benefit of smoking cessation in stroke prevention. There is a lack of interventional studies and what is less

established is the relative benefit of smoking cessation interventions (SCI~~'~~s) in the stroke population.

The purpose of this systematic review is to present up-to-date information regarding the effectiveness of SCIs for increasing cessation rates in patients with established cerebrovascular disease.

Methods

Data sources

Studies were identified from MEDLINE (1980 to Present), EMBASE (1980 to Present) and CENTRAL (May 22, 2012) databases. The following MeSH terms were used to search the MEDLINE database: "smoking cessation", "stop or quit or cease or cessation", "cerebrovascular disorders", " brain ischemia","transient ischemic attack", "brain or cerebral", "brain hemorrhage", "brain or intracranial","cerebrum or cerebral", "stroke", " brain embolism and occlusive cerebrovascular disease". Similar terms were used for EMBASE and CENTRAL databases.

Study selection

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[6] for randomized control trials. We included studies if: 1) patients were diagnosed with cerebrovascular disease by a physician or neurologist. 2) w~~W~~e applied no ethnicity or age limitations in order to be as inclusive as possible. 3) w~~W~~e also included studies that reported smoking cessation intervention conditions (behavioural, pharmacotherapy, combination therapy). ~~4)~~Finally, we excluded studies that did not report cessation rates.

Data extraction

We used a standardized form completed by two reviewers independently. We resolved discrepancies by consensus. Extracted data consisted of study characteristics (first author, year publication), patient characteristics (mean age, number of smokers, type of stroke diagnosis), type of SCI (behavioural, pharmacotherapy, combination), ~~length~~ length of follow-up of the intervention and cessation rates.

Outcome of interest

The main outcome of interest was the number of patients who quit smoking either using a smoking cessation intervention versus those who did not. Cessation rates were used from follow-up data from each study. Lost to follow-up patients were included in the denominators and were considered as smokers.

Quality of assessment of primary studies

We appraised selected articles for their methodological quality and bias using the Jadad scale.[7] The Jadad scale takes into account several methodological characteristics of clinical studies such as blinding, randomization and dropouts.[7] Scores less than 3 were considered as low quality.

~~**Statistical Analysis**~~

~~We used a mixed model Mantel-Haenszel meta-analysis approach to combine pooled effect estimates and 95% CI's were calculated. The I^2 test was used to determine whether there was statistical heterogeneity between individual studies. Comprehensive meta-analysis 2.0 statistical software was used for the analyses.~~

Results

Effect of SCI on long-term quit rates

Of 852 articles identified, 4 articles were deemed to fit the inclusion criteria. Characteristics and flow of included studies can be found in Table 1 and Figure 1 respectively. ~~The mean age of smokers was 66.5 (+/- 12.5).~~ An overall Jadad score of the selected papers was 3.75 out of a possible score of 5. With an intervention, 42 out of 176~~153~~ smokers quit versus 37 out of 178~~50~~ in the control group. This resulted in an overall cessation rate of 23.9~~28.1~~% for the intervention group compared to 20.8~~4.7~~% for the control group. ~~The meta-analysis revealed a non-significant effect of using a SCI on quitting (RR 1.19; 95% CI 0.81 to 1.73; p=0.38, I^2=0.00) (Figure 2).~~

Results of individual studies and risk of bias across studies

The first study explored the role of a patient and general practitioner systematic follow-up intervention to improve risk factor management after stroke.[8] The study recruited 523 consecutive incident stroke survivors of which 154 (29.4%) patients were identified as smokers at baseline. They were then randomized into the control (n=78) and intervention group (n=76). The overall intervention involved providing tailored evidence-based management advice to general practitioners, patients, and caregivers post-stroke. The advice consisted of treatment with antihypertensive therapy, treatment with antiplatelet therapy, and smoking cessation. Smoking cessation advice was provided in regards to nicotine replacement therapy (NRT) use .[8] The authors found that at 1 year, 21 out of ~~/~~76 (27.6%) patients in the intervention group who received smoking cessation advice in regards to NRT quit smoking. In the control group at 1 year, 22 out of ~~/~~78 (28.2%) patients successfully quit smoking.[8]

The second study explored the impact of a stroke nurse specialist's input on risk factor modification.[9] The population was selected from a clinic of ambulant patients with a diagnosis of stroke or TIA who were attending for on-going rehabilitation in a UK teaching hospital. There were 205 patients recruited, of which 78 patients were identified as smokers (38.0%). ~~There were 36/100 (36%) patients thatwere randomized into the intervention group and 42/105 (40%) were randomized into the control group.~~ The intervention consisted of meetings at 3 month intervals with a stroke nurse specialist to discuss modification of lifestyle (diet, exercise or increased activity, smoking). The control group received usual care from medical staff.[9]Upon review of this paper, it was noted that cessation rates in the original paper were not reported. We consulted the principal investigator and cessation rates are reported here from a 3 year follow-up study from McManus and associates from the original cohort.[10]Reported cessation rates in the intervention group at 42 months was found to be 1 out of ~~/36~~13 (~~7~~2.8~~0.07~~%).[10]None had quit in the control group (0 out of ~~/42~~, 0.0%~~14~~).[10]

The third study was a pilot trial of standardized counseling and cost-free pharmacotherapy for smoking cessation in secondary stroke prevention.[11]Patients who have recently experienced a TIA or stroke or have been identified as being at high risk for a cerebrovascular event were recruited and were randomized to either cost-free (CF) intervention or prescription (P) control group. Patients randomized in the CF group received free of cost medications along with counseling with a smoking cessation nurse for 26 weeks.[11] There were 255 smokers were identified and 28 participants were enrolled based on readiness to quit. The control group received usual care and prescriptions to pharmacotherapy. Cessation rates at 26 weeks for the intervention and control group was 4 out of ~~/~~15 (26.6%) and 2 out of ~~/~~13 (15.4%) respectively.[11]

The fourth study examined the difference between a minimal versus intensive smoking cessation intervention in increasing cessation rates in recruited patients with a recent stroke or TIA.[12] There were 94 smoking patients with a recent stroke or TIA that were recruited for this study.[12] For the purpose of this review, ~~and meta-analysis,~~ the ~~the minimal smoking cessation intervention was considered as the control group while the~~ intensive smoking cessation intervention was regarded as the intervention group ~~-~~ as this would be above and beyond what would be available in a 'real world' setting. To simplify the comparison group and due to the accessibility of smoking cessation counseling through a primary care physician or even a smoker's helpline, the minimal smoking cessation intervention group was considered the 'control' group. The control group consisted of a 30 minute counseling session with the study nurse advising patients to quit smoking.[12] A total of 45 patients were randomized into the control group.[12] The intervention group received five sessions of smoking cessation counseling with the study nurse while receiving free NRT.[12] A total of 49 patients were randomized into the intervention group.[12] Cessation rates at 6 months for the intervention and control group was 16 out of ~~/~~49 (32.7%) and 13 out of ~~/~~45 (28.9%) ~~and16/49 (32.7%)~~respectively.[12]

~~The methodological quality of each study scored collectively 3.75 out of 5 on the Jadad scale.~~ There were some limitations to each study. Sample size was an issue in all of the included studies. For example the small number of participants (n~~n~~ =28) in Papadakis et al.'s study meant that the study was relatively underpowered.[11] Similarly, only~~a limited~~ 94 ~~number of~~ patients were ~~(*n*=94)~~recruited in the Frandsend et al.'s study. This study saw little effect of the intensive smoking cessation intervention.[12] A larger trial would be needed to further explore the favourable trend documented in both studies. Furthermore, the provision of pharmacotherapy, counseling and follow-up may be an enhancement to 'real world' standard of care experienced by TIA and

stroke patients. A similar underpowered result due to a small sample size was observed in the study by Ellis et al./McManus et al.[9,10] They noted that the risk factor control in the control group was better than anticipated from pilot studies and in comparison to other trial evidence. Finally, all included studies recruited patients from fairly homogenous sources such as 2 GP clinics,[8] hospitals[9, 12] and a single stroke clinic,[11] which may not be generalizable to a broader stroke population in other settings.

Discussion

The purpose of this systematic review was to determine the effectiveness of SCIs in increasing cessation rates in patients with established cerebrovascular disease.

Our results demonstrate that there ~~was~~were a limited number of reported interventional studies that explore this area of stroke prevention. ~~which may have contributed to the lack of statistical significance in our meta-analyses.~~ Furthermore, there seems to be a lack of ~~evidence based~~evidence-based implementation of proven SCIs. There is a link between sub-optimal use of evidence-based smoking cessation medications and pharmacotherapy to poorer rates of smoking abstinence.[11] We found that only two of the four interventional studies[11,12] implemented evidence based approaches to smoking cessation. The approach that these studies took fell in line with recommendations outlined in the *Clinical Practice Guideline: Treating Tobacco Use and Dependence: 2008 Update.*[13]

Fiore and associates[13] suggested that effective smoking interventions consist of pharmacotherapy coupled with counseling and follow-up. First line pharmacotherapy such as NRT, Buproprion and Varenicline can double or even triple the likelihood of long-term smoking

abstinence for heavy smokers (who consume > 10 cigarettes per day) when coupled with behavioural counseling and follow-up.[14-16]

Smoking cessation interventions have been demonstrated to be effective in other populations in particular patients with coronary heart disease (CHD). CHD patients can benefit up to an increase of 44% in their cessation rate success.[17]A decrease of the risk of mortality and non-fatal myocardial infarction by 32% and 36% respectively has also been observed using this approach.[18] Larger clinical studies need to employ evidence based approaches to smoking cessation to determine their effectiveness in smokers with cerebrovascular disease.

There are several limitations in the present study, which should be considered in any interpretation of the findings. There was a high degree of variability in~~heterogeneity among pooled data for the meta-analysis in regards t~~ regards to~~o~~ the population, intervention and outcome. ~~There was significant variability in the population of the included studies.~~ For example, an array of stroke diagnoses was found ranging from incident stroke and TIA. A meta-analysis was not conducted due to the varied ~~Pooled~~ interventions from the reported~~also varied between~~ studies. ~~p~~. Wolfe and colleagues employed pharmacotherapy and advice on the use of these pharmacotherapies ~~(8),~~[8] Ellis/McManus and associates[9, 10] used standard outpatient advice with post-discharge care from a nurse specialist. Papadakis and colleagues used cost-free pharmacotherapy with counseling support and follow-up. Finally, Frandsend et al.[11] ~~,~~ used intensive counseling support with cost-free pharmacotherapy. Given these differences in interventions and that each study was set in different countries (United Kingdom, Canada and Denmark), would not have provided meaningful results from a meta-analysis. The duration of follow-up was also different amongst the included studies ranging from 3 to 42 months. Finally, cessation was only quantified biochemically by only two studies.[11, 12] Wolfe and associates[8] used

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both biochemical assays along with self-reported smoking status to quantify cessation. However, these authors only used the biochemical assays to determine the amount of misreporting in self-reported data and did not correct misreported smoking status.[8] Ellis and colleagues did not report how cessation was quantified.[9]

Conclusion

The paper provided results from a systematic review that explored the effectiveness of SCI's for increasing cessation rates. We found a limited number of reported studies that explored this area of secondary stroke prevention. Furthermore, of those interventional studies that were found, only two studies implemented evidence-based approaches in smoking cessation. A meta-analysis was not conducted due to the variability of interventions in the reported studies. Larger studies with ~~uniform~~homogenous interventions are needed to determine how effective SCI's are in increasing cessation in smokers with established cerebrovascular disease.

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Figure 1: Exclusion criteria and paper selection procedure

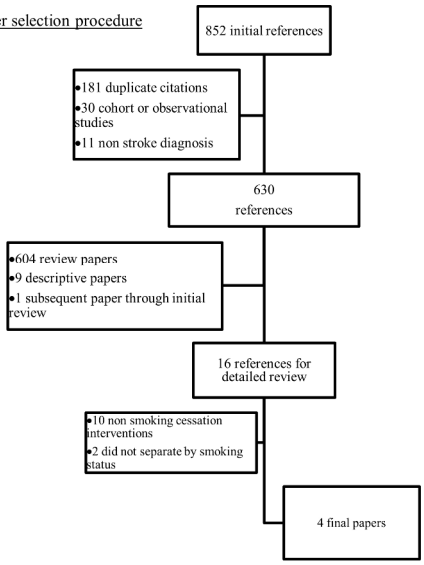

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Table 1: Characteristics of included studies

Study identification	Type of SCI/Control	Patient Characteristics	Jadad score	Cessation rate
Wolfe et al. [8]	SCI: Advice on NRT use Control: Usual care Follow-up: 1 year	Intervention: 61 (22.3%) over 80 years, 126 (46.2%) female, 76 (27.9%) smokers. Control: 50 (20.2%) over 80 years, 118 (47.8%) female, 78 (32.2%) smokers.	3	Nintervention=21 out of 76 (27.6%) Ncontrol=22 out of 78 (28.2%)
Ellis et al.[9]/McManus et al.[10]	SCI: Discussion with nurse specialist on lifestyle modification in regards to smoking cessation Control: Usual care Follow-up: 42 months	Intervention: 64.3 (62.4-66.1, 95% CI) mean age, 54 (54.0%) male, 36 (36.0%) smokers. Control: 65.8 (64.0-67.5 95% CI) mean age, 52 (49.5%) male, 42 (40.0%) smokers.	4	Nintervention =1 out of 36 (2.8%) Ncontrol=0 out of 42 (0.0%)

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Table 1: Characteristics of included studies cntd.

Study identification	Type of SCI/Control	Patient Characteristics	Study Quality (Jadad score)	Cessation rate
Papadakis et al.[11]	SCI: Counseling and cost free quit smoking medications (NRT, Bupropion, Varenicline) with follow-up Control: Usual care + prescriptions to pharmacotherapy Follow-up: 26 weeks	Intervention: 55.4 (12.4 SD) mean age, 53.3% male, 15 (53.6%) smokers. Control: 53.5 (8.1 SD), mean age, 69.2% male, 13 (46.4%) smokers.	4	Nintevention=4 out of 15 (26.6%) Ncontrol=2 out of 13 (15.4%)
Frandsend et al.[12]	SCI: Counseling and cost-free NRT (gum, tablets, patches, nasal spray) with follow-up Control: 1 time 30 min counseling support Follow-up: 6 months	Intervention: 29 (59.2%) age 50-65, 17 (34.7%) female, 49 smokers. Control: 21 (46.7%) 50-65 age, 22 (48.9%) female, 45 smokers.	4	Nintervention=16 out of 49 (32.7%) Ncontrol=13 out of 45 (28.9%)

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