Article

Comparison of Treatment Rates of Depression After Stroke Versus Myocardial Infarction: A Systematic Review and Meta-Analysis of Observational Data

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Title: Comparison of treatment rates in depression after stroke versus myocardial infarction. A systematic review and meta-analysis of observational data.

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Abstract

Objective: Depression after stroke and myocardial infarction are common but often assumed to be undertreated without reliable evidence being available. Thus, we aimed to determine treatment rates and investigate the application of guidelines in these conditions.

Methods: Databases MEDLINE, EMBASE, PsycInfo, Web of Science, CINAHL, and Scopus were systematically searched without language restriction from inception to 06/30/2017. Prospective observational studies with consecutive recruitment reporting any antidepressant treatment in adults with depression after stroke or myocardial infarction were included. Random effects models were used to calculate pooled estimates of treatment rates.

Results: 55 studies reported 32 stroke cohorts (*n* = 8,938; pooled frequency of depression = 34%, 95% CI 29 to 38%) and 17 myocardial infarction cohorts (*n* = 10,767; pooled frequency of depression = 24%, 95% CI 20 to 28%). In 29 stroke cohorts, 24% (95% CI 20 to 27%) of 2,280 depressed people used antidepressant medication. In 15 myocardial infarction cohorts, 14% (95% CI 8 to 19%) of 2,381 depressed people used antidepressant medication indicating a lower treatment rate than in stroke. After stroke, treatment with antidepressant medication was more frequent in moderate to severe (22%, 95% CI 14 to 29%) than in mild depression (9%, 95% CI 7 to 12%). Two studies reported use of psychosocial interventions, indicating that < 10% of participants were treated.

Conclusions: Despite the high frequency of depression after stroke and myocardial infarction and the existence of efficacious treatment strategies, people often remain untreated. Strategies to increase the use of efficacious treatments are needed.

Keywords: depression, stroke, myocardial infarction, treatment, pharmacoepidemiology

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List of acronyms

ADT(s) – Antidepressant drug(s)

BDI(-II) – Beck Depression Inventory(-II)

CI – Confidence interval

DSM – Diagnostic and Statistical Manual of Mental Disorders

ICD – International Classification of Diseases

MeSH – Medical Subject Headings

MI – Myocardial infarction

OECD – Organisation for Economic Co-operation and Development

PMID – Post-myocardial infarction depression

PSD – Post-stroke depression

SSRIs – Selective Serotonin Reuptake Inhibitors

WHO – World Health Organization

Introduction

Stroke and myocardial infarction (MI) are among the most common causes of disability worldwide and their burden is likely to increase (1, 2). Both diseases share a sudden onset, a threat to life (3), a need for long term rehabilitation (4, 5), and similar lifestyle risk factors (6). Additionally, depression affects 31% of all people at any time up to five years after stroke (7) and 28% of all people within two years of MI (8). These conditions, referred to as post-stroke depression (PSD) and post-MI depression (PMID), have an adverse impact on rehabilitation, including impaired functional outcome, reduced quality of life, lower medication adherence, increased risk of recurrent events, and higher mortality (8-10). The efficacy of antidepressant drugs (ADTs), but not talking therapies, has been shown to be effective for the treatment of PSD, albeit with an associated increase in adverse events (11). People with PMID have been shown to benefit from ADTs and psychosocial interventions, including relaxation therapy (12, 13). Furthermore, ADTs are recommended in moderate to severe PSD and PMID while those with milder symptoms should be closely monitored (14, 15). Individual studies have also evaluated electroconvulsive therapy (11, 16), herbal medicine (14), and non-invasive brain stimulation (17), but their efficacy has not been comprehensively demonstrated.

Proof of efficacy enhances the public's beliefs about an intervention and thereby leads to better implementation (18). Nevertheless, use of ADTs is not a reliable indicator of adequate management of PSD. ADTs were found to reduce dependency, disability, neurological impairment, and pain after stroke which may be attributable to beneficial effects on drive and motivation as well as on central nervous functioning (19, 20). After MI, ~~while~~ ADTs ~~did not improve~~could not be shown to improve cardiac prognosis (21-23) which may be due to low power for detecting mortality reduction in these trials (24). However, based on the current evidence people with depression after stroke may have some indications for the prescription of ADTs, which do not apply to MI.

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Despite the high frequency of PSD and PMID and the existence of efficacious treatment strategies, it is commonly stated that these patient groups are undertreated (25-30). However, studies rarely focus on the documentation of treatment rates resulting in a lack of comprehensive evidence. Therefore, we conducted a systematic review of the frequency of antidepressant treatment in people with PSD and PMID to determine the extent of undertreatment and to examine whether evidence-based recommendations are followed.

Methods

This systematic review was undertaken according to the MOOSE guidelines for meta-analyses of observational studies (31) and reported according to the PRISMA statement (32). The protocol was prospectively registered in PROSPERO (CRD42016051232).

Study selection

We included prospective observational studies with consecutive recruitment reporting data on treatment use at any given time-point after stroke or MI. Randomized controlled trials, case-control studies, and cross-sectional studies were excluded. Cohorts were included if participants (1) were ≥ 18 years, (2) had a clinical diagnosis of stroke or MI, and (3) were assessed for depressive symptoms using defined scores on standard screening instruments or depressive disorders (minor depression, dysthymia, major depression) applying ICD or DSM criteria. Finally, studies were included if they (4) reported the frequency of use of ADTs, psychosocial interventions, herbal medicine, electroconvulsive therapy or non-invasive brain stimulation for the treatment of depression. Psychosocial interventions were defined as any treatment including telemedical or direct patient-professional interaction ranging from counselling to psychotherapy. Interventions with the sole purpose of education, information or social transfer, and occupational therapy were excluded.

Data sources and extraction

The literature search was conducted on MEDLINE, EMBASE, PsycInfo, Web of Science, CINAHL, and Scopus from inception to 06/30/2017. Databases were searched using MeSH terms and related keywords for stroke OR myocardial infarction AND depression AND prospective study design. The search strategy for MEDLINE is accessible at http://www.crd.york.ac.uk/PROSPEROFILES/51232_STRATEGY_20161010.pdf and was adjusted for other databases. After searching and excluding irrelevant studies via title and abstract, eligibility was examined using full text articles. Reference lists of included articles and related review articles were manually searched. In an attempt to access all published studies worldwide, 17 non-English articles were reviewed in full text and translated from Chinese, Czech, Danish, French, German, Portuguese, Russian, and Spanish.

Study quality was assessed by grouping studies into three categories representing completeness of case-selection (7). The first group of population-based studies, considered the highest (least biased) quality, consisted of studies that attempted to recruit all people with stroke or MI, including those not admitted to hospital for acute care. The other two categories were hospital-based studies, which included all inpatients recruited from acute care medical wards in general hospitals, and rehabilitation-based studies, which included patients from rehabilitation wards or stroke/cardiac care units. Treatment rates were also pooled and compared among WHO world regions (33) and between OECD-member and non-member countries, if applicable. Furthermore, treatment rates were pooled and compared among decades of publication (before 2000, 2000-2009, since 2010).

Study reports with evidence of overlapping recruitment sites, study dates, grant funding numbers, and similar or identical reported patient characteristics were considered to be from the same cohort. If several articles reported data from the same cohort, data were taken from the first publication of a given time-point. If multiple instruments were used to assess depressive symptoms and their treatment at the same time point, data showing the highest proportion treated were included.

All authors were contacted for missing or additional data and to confirm suspected overlapping cohorts. Additional data were included if received before 30/09/2017.

Data synthesis

Extracted data were stratified according to case selection and time of assessment after stroke or MI. Data assessed up to three months after the ictus were categorized as short-term, from three up to twelve months as medium-term and twelve months or later as long-term. Depression was categorised as mild (minor, mild depression; dysthymia) or moderate/severe (moderate, severe, major depression) according to the categories applied by study authors.

Frequencies of depressive symptoms and treatment use at the first assessment were pooled using the random effects model of DerSimonian and Laird (34). Sensitivity analyses included the comparison with fixed effect models, treatment use at last assessment, cohort size: small ($n < 100$) and large ($n > 100$), and interviewer-administered vs. self-completed questionnaires to screen for depression. Publication bias was assessed by inspecting funnel plots and conducting Egger's regression (35). Subgroup meta-analyses included patient groups with mild, moderate/severe, and no depression receiving treatment.

Results

The applied search strategies identified over 46,000 articles, of which 625 were reviewed in full-text. 32 stroke and 17 MI studies (in 55 manuscripts) were included. Authors of 20 studies provided additional unpublished data (36-55). The review process is illustrated in Figure 1.

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Description of the study samples ~~Population description~~

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People with stroke were assessed between two weeks and five years after the ictus. The minimum age criterion of ≥ 18 years could not be confirmed in seven studies (56, 66, 67, 71, 74-76). One study (59) included people ≥ 15 years of age and was included because of an assumed small number of people under 18 years and a large sample size. Further study details are listed in Table 1. The pooled frequency of PSD in 32 cohorts was 34% (95% confidence interval [CI] 29 to 38%) with significant heterogeneity among studies ($p < .001$) and a significant intercept in Egger's regression ($p < .001$) indicating that smaller studies reported higher frequencies.

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People with MI were assessed between one day and 18 months after the ictus. The age criterion could not be confirmed in three studies (79, 82, 84). Further study details are listed in Table 2. The pooled frequency of PMID in 17 cohorts was 24% (95% CI 20 to 28%) with significant heterogeneity ($p < .001$) and a non-significant intercept in Egger's regression ($p = .19$).

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Treatment of PSD

No treatment other than ADTs or psychosocial interventions were reported. One stroke study reported use of psychotherapy (none of the 89 people with PSD received psychotherapy) (60), and another reported if people were referred to a psychiatric service in addition to receiving ADTs (none of 11 people with PSD were referred) (41). The studies did not specify these treatments further. Hence, 31 studies reported use of ADTs. One of these did not report the cut-off used for depression

assessment and was excluded from analyses (55). Visual investigation of the funnel plot led to exclusion of a further study representing an outlier with small sample (62). Results of sensitivity analyses were identical if this study was in- or excluded.

Finally, 29 cohorts consisting of 8,634 people with stroke were included in random effects analyses of ADT use. Frequency of PSD in these cohorts (32%, 95% CI 27 to 37%) was not significantly different from the frequency in all 32 cohorts. The pooled estimate of ADT use was 24% (95% CI 20 to 27%) in 2,280 people with PSD with significant heterogeneity among studies ($p < .001$) and a non-significant intercept in Egger's regression ($p = .082$). Sensitivity analyses did not produce any significantly different result. The forest plot (Fig. 2) illustrates the pooled estimates for different time windows and recruitment types. There was no significant difference in treatment rates among population-based (21%, 95% CI 14 to 28%), hospital-based (21%, 95% CI 15 to 27%), and rehabilitation-based studies (28%, 95% CI 22 to 34%). Analyses comparing pooled treatment rates between cohorts from different WHO world regions (33),between OECD member and non-member countries as well as among decades of publication produced no significantly different results.

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Data on ADT use could be extracted from three cohorts with mild depression (41, 42, 71) and six cohorts with moderate to severe depression (37, 39, 41, 42, 67, 71). ADTs were significantly less often used in PSD with mild depression (9%, 95% CI 7 to 12%) than in PSD with moderate to severe depression (22%, 95% CI 14 to 29%). Heterogeneity of studies was not significant in either group ($p > .30$).

Furthermore, twelve studies reported ADT use in non-depressed people with stroke (39-41, 54, 57, 58, 64, 69-71, 75, 77). The pooled estimate of these frequencies was 11% (95% CI 7 to 14%) with

significant heterogeneity among studies ($p < .001$) and a non-significant intercept in Egger's regression ($p > .90$). Additionally, one study reported that 18% of those not depressed and treated at 12 months were previously depressed at 3 months (57) and one study reported that 64% who were not depressed and treated at 6 months were previously depressed at 7 weeks (54).

Treatment of PMID

No treatment other than ADTs or psychosocial interventions were reported. One study reported the use of psychopharmacology and/or psychotherapy by 3 of 5 with PMID (60.0%) (78), one study reported use of psychiatric treatment by 3 of 18 with PMID (16.6%) (82), and one study reported use of psychosocial interventions for depression by 72 of 759 with PMID (9.5%) (81) without further description of these interventions.

The 15 studies reporting use of ADTs consisted of 10,635 with MI who were included in the random effects analyses. The pooled frequency of PMID in these cohorts (25%, 95% CI 21 to 30%) was not significantly different from the frequency in all 17 cohorts. The pooled frequency of ADT use was 14% (95% CI 8 to 19%) in 2,381 with PMID and hence, significantly lower than in PSD. Heterogeneity among studies was significant ($p < .001$) with a non-significant intercept in Egger's regression ($p = .062$). The estimate did not change in sensitivity analyses. Furthermore, people in hospital-based studies received ADTs more often (19%, 95% CI 15 to 24%) than people in rehabilitation-based studies (8%, 95% CI 4 to 13%). The ten short-term studies showed a pooled frequency of 16% (95% CI 11 to 21%) (44, 45, 48-53, 80, 81), the three medium-term studies a frequency of 12% (95% CI 0 to 25%) (46, 83, 84), and the two long-term studies a frequency of 6% (95% CI 1 to 10%) (47, 79) demonstrating a significant difference between frequencies in the short- and the two long-term rehabilitation-based studies. Comparing pooled treatment rates between cohorts from the European region and the region of the Americas as well as among decades of publication yielded no significant difference.

Discussion

This meta-analysis provides the first comprehensive evidence of depression treatment rates after stroke and myocardial infarction. Although more PSD cohorts could be identified, PMID cohorts were usually larger resulting in similar numbers of people being included. The frequencies of depressive symptoms were in the same range as in other systematic reviews on PSD (7) and PMID (8), supporting the generalisability of our findings. Only a few study authors reported the use of treatments other than ADTs (41, 60, 78, 81, 82). This may be explained by the lack of evidence of other efficacious treatments for people with PSD (11), whereas pharmacological and ~~psychological~~ psychosocial interventions have proven efficacious for PMID ~~-~~(12). This may also be due to the investigation of more innovative interventions in PMID like ~~e.g.~~ the telephone-based collaborative care program of the MOSAIC trial (85). ~~-~~As only few or no people used psychosocial interventions in the studies reporting these treatments and use of psychosocial interventions may be documented less often in outpatient settings, this finding may also be attributed to reporting and measurement biases.

Every fourth person with PSD and every seventh person with PMID reported using ADTs indicating that only a small proportion of people with depression after stroke and MI receives evidence-based treatment. Clinical trials have proven the efficacy of ADTs in both disorders (11, 12) but they are only effective if they are prescribed and taken (18). Additionally, some studies indicate higher mortality in people with untreated PSD and PMID (81, 86). However, the ENRICHD trial did not show a reduction of late mortality in people with PMID who were treated with cognitive behavioral therapy and sertraline but demonstrated increased late mortality in people whose depression is refractory to treatment (22). Possible reasons for undertreatment include insufficient assessment and follow-up of psychological status (47, 87) as well as uncertainty due to comorbidities and polypharmacy, which is common in people with stroke and MI (25). Furthermore, depression may

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be perceived as a natural reaction to stroke or MI which therefore is assumed to require no further treatment (88). Depressive symptoms such as lack of energy, hopelessness and withdrawal may also contribute to people stopping rehabilitation, follow-up visits and medications (46). Additionally, patients may want to avoid the label and associated stigma of mental illness and therefore, withdraw from treatment (89). Frequency of treatment was not different based on case selection in PSD, indicating similar health care practices across all settings. Treatment rates in rehabilitation-based PMID cohorts were significantly lower than in hospital-based cohorts, which contrasts especially with stroke cohorts showing the descriptively highest frequency of treatment in rehabilitation settings. The difference between MI cohorts may be attributable to better access of people with MI to mental health professionals in hospital compared to rehabilitation due to counselei~~l~~ service. Although guidelines list psychological evaluation as an essential part of cardiac rehabilitation (84), evidence suggests low psychological expertise in this setting (85). While cardiac rehabilitation usually focuses on the prevention of recurrent events using pharmacological and lifestyle interventions (84), stroke rehabilitation includes neuropsychological assessment and treatment of cognitive impairment (86). Therefore, mental health expertise may be higher in hospital and stroke rehabilitation compared to cardiac rehabilitation possibly resulting in better recognition and treatment of depressive symptoms. Treatment rates in PSD and PMID did not differ between world regions (33) or by OECD membership where most cohorts were from Europe, North America and/or OECD countries. Additionally, treatment rates did not differ depending on year of publication despite major developments in the health care of people with stroke and MI over the last decades. Three studies (37, 40, 69) distinguishing classes of ADTs reported SSRIs being most frequently used in PSD which is in line with research favoring SSRIs as a pharmacological treatment (19).

PSD was more frequently treated than PMID and a tenth of non-depressed people received ADTs after stroke. This may be based on the clinical consideration of findings supporting the efficacy of

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ADTs for physical and functional rehabilitation after stroke (19, 20). Additionally, people with more severe PSD received ADTs more frequently which is in keeping with evidence-based guideline recommendations (15), better recognition (90), and higher need (91).

While our findings are limited by the high variability of the assessment tools used, criteria for depressive symptoms, assessment times, methods for collecting data on treatment use, and the selection criteria within the cohorts, they remain consistent in sensitivity analyses. As a further strength of this meta-analysis, we included many unpublished data sets which were provided by original authors. However, it must be noted that the reported use of antidepressants may not indicate adequate treatment of depression as they may also be described to improve physical and functional rehabilitation or treat anxiety (19, 20). Furthermore, this meta-analysis excluded interventions solely providing information or education as they were not investigated in randomized controlled trials up to now. Nevertheless, people with PSD or PMID may benefit from these interventions. Finally, many cohorts had to be excluded as they assessed depressive symptoms in cohorts of people with coronary diseases generally, rather than solely MI. We are unclear if, or to what extent, this may bias our results.

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While the specific determinants of treatment use in PSD and PMID may need further investigation, the considerable undertreatment found in our study indicates a need for screening for depression after stroke and MI (8, 9) and clear management protocols which include reassessment and stopping guidelines for use in healthcare settings. As guidelines already include similar recommendations (9, 14, 15), specific education of health professionals is essential to close the gap to clinical practice, increase treatment rates, and thereby reduce the significant burden of PSD and PMID globally (1).

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Figure captions

Fig.1 PRISMA flow diagram of literature review process

Fig.2 Forest plot of antidepressant drug treatment in people with post-stroke depression

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