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

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Ladwig, Simon, Zhou, Zien, Xu, Ying, Wang, Xia, Chow, Clara K., Werheid, Katja and Hackett, Maree ORCID: 0000-0003-1211-9087 (2018) Comparison of Treatment Rates of Depression After Stroke Versus Myocardial Infarction: A Systematic Review and Meta-Analysis of Observational Data. Psychosomatic Medicine, 80 (8). pp. 754-763. ISSN 0033-3174

It is advisable to refer to the publisher's version if you intend to cite from the work.
<http://dx.doi.org/10.1097/PSY.0000000000000632>

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

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26 Word count: 5.932

27 Tables: 2

28 Figures: 2

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Treatment rates in PSD and PMID

1 Conflict of Interest and Source of Funding

2 Simon Ladwig was in receipt of the Humboldt Research Track Scholarship (2016-2017). Zien Zhou
3 held an overseas visiting funding from Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong
4 University (2016–2018) and a Scientia PhD Scholarship from the UNSW Sydney (2018–2022).
5 Clara Chow was supported by National Health and Medical Research Council Career Development
6 Fellowship (Level 2) (APP1105447) and co-funded by a Heart Foundation Future Leader
7 Fellowship. Maree Hackett was in receipt of a National Heart Foundation (Australia) Future Leader
8 Fellowship #100034 Level 2, 2014-2017) and a National Health and Medical Research Council
9 Career Development Fellowship, Level 2 (APP1141328, 2018-2021). Other co-authors have no
10 interests or funding to disclose.

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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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Treatment rates in PSD and PMID

- 1
- 2
- 3 ADT(s) – Antidepressant drug(s)
- 4 BDI(-II) – Beck Depression Inventory(-II)
- 5 CI – Confidence interval
- 6 DSM – Diagnostic and Statistical Manual of Mental Disorders
- 7 ICD – International Classification of Diseases
- 8 MeSH – Medical Subject Headings
- 9 MI – Myocardial infarction
- 10 OECD – Organisation for Economic Co-operation and Development
- 11 PMID – Post-myocardial infarction depression
- 12 PSD – Post-stroke depression
- 13 SSRIs – Selective Serotonin Reuptake Inhibitors
- 14 WHO – World Health Organization
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List of acronyms

Treatment rates in PSD and PMID

Introduction

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

16
17 Proof of efficacy enhances the public's beliefs about an intervention and thereby leads to better
18 implementation (18). Nevertheless, use of ADTs is not a reliable indicator of adequate management
19 of PSD. ADTs were found to reduce dependency, disability, neurological impairment, and pain after
20 stroke which may be attributable to beneficial effects on drive and motivation as well as on central
21 nervous functioning (19, 20). After MI, while ADTs did not improve could not be shown to improve
22 cardiac prognosis (21-23) which may be due to low power for detecting mortality reduction in these
23 trials (24). However, based on the current evidence people with depression after stroke may have
24 some indications for the prescription of ADTs, which do not apply to MI.

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Treatment rates in PSD and PMID

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

7 Methods

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

11 Study selection

12 We included prospective observational studies with consecutive recruitment reporting data on
13 treatment use at any given time-point after stroke or MI. Randomized controlled trials, case-control
14 studies, and cross-sectional studies were excluded. Cohorts were included if participants (1) were \geq
15 18 years, (2) had a clinical diagnosis of stroke or MI, and (3) were assessed for depressive symptoms
16 using defined scores on standard screening instruments or depressive disorders (minor depression,
17 dysthymia, major depression) applying ICD or DSM criteria. Finally, studies were included if they
18 (4) reported the frequency of use of ADTs, psychosocial interventions, herbal medicine,
19 electroconvulsive therapy or non-invasive brain stimulation for the treatment of depression.
20 Psychosocial interventions were defined as any treatment including telemedical or direct patient-
21 professional interaction ranging from counselling to psychotherapy. Interventions with the sole
22 purpose of education, information or social transfer, and occupational therapy were excluded.

23

Treatment rates in PSD and PMID

1 Data sources and extraction

2 The literature search was conducted on MEDLINE, EMBASE, PsycInfo, Web of Science, CINAHL,
3 and Scopus from inception to 06/30/2017. Databases were searched using MeSH terms and related
4 keywords for stroke OR myocardial infarction AND depression AND prospective study design. The
5 search strategy for MEDLINE is accessible at [http://www.crd.york.ac.uk/PROSPEROFILES/
6 51232_STRATEGY_20161010.pdf](http://www.crd.york.ac.uk/PROSPEROFILES/51232_STRATEGY_20161010.pdf) and was adjusted for other databases. After searching and
7 excluding irrelevant studies via title and abstract, eligibility was examined using full text articles.
8 Reference lists of included articles and related review articles were manually searched. In an attempt
9 to access all published studies worldwide, 17 non-English articles were reviewed in full text and
10 translated from Chinese, Czech, Danish, French, German, Portuguese, Russian, and Spanish.
11 Study quality was assessed by grouping studies into three categories representing completeness of
12 case-selection (7). The first group of population-based studies, considered the highest (least biased)
13 quality, consisted of studies that attempted to recruit all people with stroke or MI, including those not
14 admitted to hospital for acute care. The other two categories were hospital-based studies, which
15 included all inpatients recruited from acute care medical wards in general hospitals, and
16 rehabilitation-based studies, which included patients from rehabilitation wards or stroke/cardiac care
17 units. Treatment rates were also pooled and compared among WHO world regions (33) and between
18 OECD-member and non-member countries, if applicable. Furthermore, treatment rates were pooled
19 and compared among decades of publication (before 2000, 2000-2009, since 2010).
20 Study reports with evidence of overlapping recruitment sites, study dates, grant funding numbers,
21 and similar or identical reported patient characteristics were considered to be from the same cohort.
22 If several articles reported data from the same cohort, data were taken from the first publication of a
23 given time-point. If multiple instruments were used to assess depressive symptoms and their
24 treatment at the same time point, data showing the highest proportion treated were included.

Treatment rates in PSD and PMID

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

3 Data synthesis

4 Extracted data were stratified according to case selection and time of assessment after stroke or MI.

5 Data assessed up to three months after the ictus were categorized as short-term, from three up to
6 twelve months as medium-term and twelve months or later as long-term. Depression was categorised
7 as mild (minor, mild depression; dysthymia) or moderate/severe (moderate, severe, major
8 depression) according to the categories applied by study authors.

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

16 Results

17 The applied search strategies identified over 46,000 articles, of which 625 were reviewed in full-text.
18 32 stroke and 17 MI studies (in 55 manuscripts) were included. Authors of 20 studies provided
19 additional unpublished data (36-55). The review process is illustrated in Figure 1.

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21 ----- INSERT [FIG. 1] ABOUT HERE-----
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Treatment rates in PSD and PMID

1 Description of the study samples ~~Population description~~

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

9
10 ----- INSERT [TABLE 1] ABOUT HERE-----

11
12 People with MI were assessed between one day and 18 months after the ictus. The age criterion
13 could not be confirmed in three studies (79, 82, 84). Further study details are listed in Table 2. The
14 pooled frequency of PMID in 17 cohorts was 24% (95% CI 20 to 28%) with significant
15 heterogeneity ($p < .001$) and a non-significant intercept in Egger's regression ($p = .19$).

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17 ----- INSERT [TABLE 2] ABOUT HERE-----

18
19 Treatment of PSD

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

Treatment rates in PSD and PMID

1 assessment and was excluded from analyses (55). Visual investigation of the funnel plot led to
2 exclusion of a further study representing an outlier with small sample (62). Results of sensitivity
3 analyses were identical if this study was in- or excluded.
4 Finally, 29 cohorts consisting of 8,634 people with stroke were included in random effects analyses
5 of ADT use. Frequency of PSD in these cohorts (32%, 95% CI 27 to 37%) was not significantly
6 different from the frequency in all 32 cohorts. The pooled estimate of ADT use was 24% (95% CI 20
7 to 27%) in 2,280 people with PSD with significant heterogeneity among studies ($p < .001$) and a
8 non-significant intercept in Egger's regression ($p = .082$). Sensitivity analyses did not produce any
9 significantly different result. The forest plot (Fig. 2) illustrates the pooled estimates for different time
10 windows and recruitment types. There was no significant difference in treatment rates among
11 population-based (21%, 95% CI 14 to 28%), hospital-based (21%, 95% CI 15 to 27%), and
12 rehabilitation-based studies (28%, 95% CI 22 to 34%). Analyses comparing pooled treatment rates
13 between cohorts from different WHO world regions (33), between OECD member and non-member
14 countries as well as among decades of publication produced no significantly different results.

15
16 ----- INSERT [FIG. 2] ABOUT HERE -----

17
18 Data on ADT use could be extracted from three cohorts with mild depression (41, 42, 71) and six
19 cohorts with moderate to severe depression (37, 39, 41, 42, 67, 71). ADTs were significantly less
20 often used in PSD with mild depression (9%, 95% CI 7 to 12%) than in PSD with moderate to severe
21 depression (22%, 95% CI 14 to 29%). Heterogeneity of studies was not significant in either group (p
22 $> .30$).

23 Furthermore, twelve studies reported ADT use in non-depressed people with stroke (39-41, 54, 57,
24 58, 64, 69-71, 75, 77). The pooled estimate of these frequencies was 11% (95% CI 7 to 14%) with

Treatment rates in PSD and PMID

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

5 Treatment of PMID

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

11 The 15 studies reporting use of ADTs consisted of 10,635 with MI who were included in the random
12 effects analyses. The pooled frequency of PMID in these cohorts (25%, 95% CI 21 to 30%) was not
13 significantly different from the frequency in all 17 cohorts. The pooled frequency of ADT use was
14 14% (95% CI 8 to 19%) in 2,381 with PMID and hence, significantly lower than in PSD.

15 Heterogeneity among studies was significant ($p < .001$) with a non-significant intercept in Egger's
16 regression ($p = .062$). The estimate did not change in sensitivity analyses. Furthermore, people in
17 hospital-based studies received ADTs more often (19%, 95% CI 15 to 24%) than people in
18 rehabilitation-based studies (8%, 95% CI 4 to 13%). The ten short-term studies showed a pooled
19 frequency of 16% (95% CI 11 to 21%) (44, 45, 48-53, 80, 81), the three medium-term studies a
20 frequency of 12% (95% CI 0 to 25%) (46, 83, 84), and the two long-term studies a frequency of 6%
21 (95% CI 1 to 10%) (47, 79) demonstrating a significant difference between frequencies in the short-
22 and the two long-term rehabilitation-based studies. Comparing pooled treatment rates between
23 cohorts from the European region and the region of the Americas as well as among decades of
24 publication yielded no significant difference.

Discussion

1
2 This meta-analysis provides the first comprehensive evidence of depression treatment rates after
3 stroke and myocardial infarction. Although more PSD cohorts could be identified, PMID cohorts
4 were usually larger resulting in similar numbers of people being included. The frequencies of
5 depressive symptoms were in the same range as in other systematic reviews on PSD (7) and PMID
6 (8), supporting the generalisability of our findings. Only a few study authors reported the use of
7 treatments other than ADTs (41, 60, 78, 81, 82). This may be explained by the lack of evidence of
8 other efficacious treatments for people with PSD (11), whereas pharmacological and **psychological**
9 **psychosocial** interventions have proven efficacious for PMID-(12). **This may also be due to the**
10 **investigation of more innovative interventions in PMID like e.g. the telephone-based collaborative**
11 **care program of the MOSAIC trial (85).** -As only few or no people used psychosocial interventions
12 in the studies reporting these treatments and use of psychosocial interventions may be documented
13 less often in outpatient settings, this finding may also be attributed to reporting and measurement
14 biases.
15 Every fourth person with PSD and every seventh person with PMID reported using ADTs indicating
16 that only a small proportion of people with depression after stroke and MI receives evidence-based
17 treatment. Clinical trials have proven the efficacy of ADTs in both disorders (11, 12) but they are
18 only effective if they are prescribed and taken (18). Additionally, **some** studies indicate higher
19 mortality in people with untreated PSD and PMID (81, 86). **However, the ENRICHD trial did not**
20 **show a reduction of late mortality in people with PMID who were treated with cognitive behavioral**
21 **therapy and sertraline but demonstrated increased late mortality in people whose depression is**
22 **refractory to treatment (22).** Possible reasons for undertreatment include insufficient assessment and
23 follow-up of psychological status (47, 87) as well as uncertainty due to comorbidities and
24 polypharmacy, which is common in people with stroke and MI (25). Furthermore, depression may

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Treatment rates in PSD and PMID

1 be perceived as a natural reaction to stroke or MI which therefore is assumed to require no further
2 treatment (88). Depressive symptoms such as lack of energy, hopelessness and withdrawal may also
3 contribute to people stopping rehabilitation, follow-up visits and medications (46). Additionally,
4 patients may want to avoid the label and associated stigma of mental illness and therefore, withdraw
5 from treatment (89). Frequency of treatment was not different based on case selection in PSD,
6 indicating similar health care practices across all settings. Treatment rates in rehabilitation-based
7 PMID cohorts were significantly lower than in hospital-based cohorts, which contrasts especially
8 with stroke cohorts showing the descriptively highest frequency of treatment in rehabilitation
9 settings. The difference between MI cohorts may be attributable to better access of people with MI to
10 mental health professionals in hospital compared to rehabilitation due to **counseling** service. Although
11 guidelines list psychological evaluation as an essential part of cardiac rehabilitation (84), evidence
12 suggests low psychological expertise in this setting (85). While cardiac rehabilitation usually focuses
13 on the prevention of recurrent events using pharmacological and lifestyle interventions (84), stroke
14 rehabilitation includes neuropsychological assessment and treatment of cognitive impairment (86).
15 Therefore, mental health expertise may be higher in hospital and stroke rehabilitation compared to
16 cardiac rehabilitation possibly resulting in better recognition and treatment of depressive symptoms.
17 Treatment rates in PSD and PMID did not differ between world regions (33) or by OECD
18 membership where most cohorts were from Europe, North America and/or OECD countries.
19 Additionally, treatment rates did not differ depending on year of publication despite major
20 developments in the health care of people with stroke and MI over the last decades. Three studies
21 (37, 40, 69) distinguishing classes of ADTs reported SSRIs being most frequently used in PSD
22 which is in line with research favoring SSRIs as a pharmacological treatment (19).
23 PSD was more frequently treated than PMID and a tenth of non-depressed people received ADTs
24 after stroke. This may be based on the clinical consideration of findings supporting the efficacy of

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Treatment rates in PSD and PMID

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

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

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16 While the specific determinants of treatment use in PSD and PMID may need further investigation,
17 the considerable undertreatment found in our study indicates a need for screening for depression after
18 stroke and MI (8, 9) and clear management protocols which include reassessment and stopping
19 guidelines for use in healthcare settings. As guidelines already include similar recommendations (9,
20 14, 15), specific education of health professionals is essential to close the gap to clinical practice,
21 increase treatment rates, and thereby reduce the significant burden of PSD and PMID globally (1).

1

Acknowledgments

2 The authors would like to thank all corresponding study authors for providing additional data and
3 information. We also thank Mansur Kutlubaev (Russian), Lorena Ataíde Lopes (Portuguese), and
4 Marek Čontošfalský (Czech) for translating non-English language articles.

5

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Figure captions

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- 3 **Fig.1** PRISMA flow diagram of literature review process
- 4 **Fig.2** Forest plot of antidepressant drug treatment in people with post-stroke depression
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