Full Title: Frequency of Anxiety After Stroke: A Systematic Review and Meta-Analysis of Observational Studies

Cover Title: Anxiety after stroke

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Abstract

Background and purpose

Negative psychological outcomes occur frequently after stroke, however there is uncertainty regarding the occurrence of anxiety disorders and anxiety symptoms after stroke. A systematic review of observational studies was conducted that assessed the frequency of anxiety in stroke patients using a diagnostic or screening tool.

Summary of review

Databases were searched up to March 2011. A random effects model was used to summarize the pooled estimate. Statistical heterogeneity was assessed using the I^2 statistic. Forty-four published studies comprising 5,760 stroke patients were included. The overall pooled estimate of anxiety disorders assessed by clinical interview was 18% (95%CI 8% - 29%, I^2 = 97%), and was 25% (95% CI 21%-28%, I^2 = 90%) for anxiety assessed by rating scale. The Hospital Anxiety and Depression Scale- Anxiety subscale (HADS-A) probable and possible cut-off scores were the most widely used assessment criteria. The combined rate of anxiety by time after stroke was: 20% (95% CI 13%-27%, I^2 = 96%) within one month of stroke; 23% (95% CI 19%-27%, I^2 = 84%) 1 to 5 months after stroke; and 24% (95% CI 19%-29%, I^2 = 89%) 6 months or more after stroke.

Conclusion

Anxiety after stroke occurs frequently although methodological limitations in the primary studies may limit generalizability. Given the association between prevalence

rates and the HADS-A cut-off used in studies, reported rates could in fact under-represent the extent of the problem. Additionally risk factors for anxiety, its impact on patient outcomes, and effects in tangent with depression remain unclear.

Introduction

Globally, anxiety disorders are the most common mental health problem (1). In some instances anxiety is functionally appropriate and even advantageous when it prompts protective health behavior, and a certain level would be considered a normal reaction to experiencing a life threatening event such as stroke. However, anxiety disorders and substantially elevated levels of anxiety symptoms are associated with reduced quality of life (2), lead to increased healthcare utilization, and risk of disabling health conditions (3, 4), and may even augment risk of death (5).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)(6) classifies anxiety disorders as a collection of individual syndromes that include generalized anxiety disorder (GAD), panic disorder (with or without agoraphobia), agoraphobia (with or without panic), specific phobia, social phobia, obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, anxiety disorder due to a general medical condition, substance induced anxiety disorder, and anxiety disorder not otherwise specified. Each disorder has certain distinct features yet they all share similar hallmark characteristics of excessive and irrational fear, feeling apprehensive and tense,

and difficulty and distress in managing daily tasks. Certain physiological symptoms such as palpitations, dizziness or trembling may also be present.

Anxiety has received substantially less attention relative to other psychological problems that occur post-stroke (7-9). Several reasons attribute to its neglect. Early population-based prevalence studies found that the frequency of anxiety disorders after stoke was low (10). This would seem to be in keeping with epidemiologic studies in the general adult population that suggest that anxiety disorders are uncommon among older adults, and approximately three quarters of stroke patients are over 65 years of age (11). However, one of the diagnostic challenges for assessing mood in stroke patients is that some symptoms of disorder, such as sleep disturbance or fatigue, are common consequences of stroke itself. This may have the effect of falsely reducing reported rates of mood disorder when using DSM criteria (12).

As a result of these diagnostic challenges the study of anxiety symptoms assessed by rating scales and not meeting full DSM criteria has proved extremely relevant. Studies have shown that people with sub-threshold symptoms and diagnosed anxiety disorders are similarly affected by the anxiety (12). Many stroke patients report substantial fears (possibly indicative of phobic disorders) about recurrent stroke, falling, or returning to work (13-15) that would be unlikely to constitute diagnosis of an anxiety or related mental health disorder, yet appear to impact significantly on daily living.

Additionally co-morbidity of anxiety and depression is well documented (16). Traditional diagnostic and treatment approaches have used a hierarchical approach

with depressive symptoms taking precedence. Further, some argue that certain forms of anxiety should be conceptualized as a residual or severity marker of depression (17). However, factor analysis has found that anxiety and depression appear to be distinct (16, 18) (19), and a differential response to treatment between the two conditions has been observed (20). The extent to which anxiety is a problem after stroke is uncertain. The aim of this review was to estimate the frequency of anxiety disorders after stroke. We were also interested in the frequency of anxiety 'caseness' as determined by a score on anxiety rating scales. A robust estimate of post-stroke anxiety prevalence is needed to assess its potential impact and highlight treatment needs. _ENREF_18

METHODS

Inclusion / exclusion criteria

The review included studies in populations or groups of patients who had a clinical diagnosis of ischemic or hemorrhagic stroke or transient ischemic attack (TIA), and were diagnosed with an anxiety disorder, or assessed for anxiety symptoms on a rating scale such as the Hospital Anxiety and Depression Scale (HADS). Non-English language papers that were potentially eligible based on their title or abstract were translated. Studies were excluded if they: (1) were intervention studies; (2) were limited to patients with subarachnoid hemorrhage or other select characteristic such as gender; (3) used non-specific measures of psychological distress but not designed to screen expressly for an anxiety; (4) involved retrospective recruitment or reporting of mood; (5) used convenience sampling; (6) reported anxiety as a continuous outcome

and we were unable to obtain a categorical assessment from the author or; (7) measured anxiety by proxy.

Study identification and data extraction

Electronic searches in MEDLINE, EMBASE, PsycINFO, Allied and Complementary Medicine, CINAHL, and Proquest dissertation were conducted using the terms “stroke” or “cerebrovascular disorders” or “cerebrovascular accident” in combination with “anxiety disorders”, or “adjustment disorders”, or “neurotic disorders”, or “mental disorders”, or “worry”, or “fear”. We combined the search terms with the “explode” feature and no language restrictions were put in place (see Appendix 1 for detailed search strategy). One investigator (ACB) conducted the initial search from database inception to March, 2010 and updated it up to March, 2011. Reference lists from included studies were checked, and study authors were contacted for additional data where necessary.

One reviewer (ACB) screened and identified studies against the selection criteria. A second reviewer (PK) conducted a random check of approximately 10% of titles and abstracts to check reliability of initial screening. Independent data extraction by two reviewers (ACB and PK) was performed for all eligible studies.

Quality of evidence

Information about study design, setting, and patient characteristics was extracted. Study quality was assessed using a modified version of the tool for systematic reviews of observational studies (QATSO)(21) and each study was evaluated based on the

method of recruitment into study, instrument used to measure anxiety, proportion of eligible patients who participated, proportion lost to follow-up (if applicable), and adequacy of descriptive details about the study populations. At a minimum it was expected that age and sex would be reported.

Data synthesis

Studies were grouped into four categories based on method of case ascertainment. *Population-based studies* which attempted to recruit all stroke survivors in a particular geographical area over a given period of time. These are regarded as the least biased method to identify cases in cohort studies. *Hospital-* and *rehabilitation-based studies* that recruited in-patients,or those attending rehabilitation facilities. Lastly *community-based studies* that recruited patients who were not in hospital or rehabilitation facilities and made no attempt to include all stroke cases in the geographic area (e.g. only patients from select general practices were included). Studies were also stratified by three time periods: the “acute phase” (defined as less than one month post-stroke), “mid-term phase” (one to five months post-stroke), and “long-term phase” (six or more months post-stroke).

Several meta-analyses were conducted. Studies using the DSM-III (80) were excluded from the pooled result as this classification system adheres to a strict hierarchical rule no longer used in practice, whereby anxiety is not diagnosed in the presence of depression. For studies that used rating scales, we accepted whatever threshold score for ‘caseness’ that had been selected by the primary researchers. In studies that measured anxiety over more than one time point, the earliest measurement

from each study was used in the meta-analysis for calculating overall prevalence rates. This was considered to be the most robust estimate, with the most complete follow-up data. Other meta-analyses stratified findings by source of study population (population; hospital, rehabilitation, or community) and time-period post-stroke and used the same inclusion criteria described above. Data were summarized using the random effects model which takes into account heterogeneity within and between studies. Chi-square was used to test for sub-group differences, and heterogeneity among the studies was assessed using the I^2 statistic. Heterogeneity is considered substantial if the I^2 statistic is greater than 50%.(22) Analysis was carried out using RevMan 5.1.

RESULTS

The search produced 21,432 references, of which 50 publications (from 41 studies) met the inclusion criteria in March 2010. Ten studies which could have potentially contributed to the review findings were excluded as authors were unavailable to provide necessary information. Reasons for exclusion were: reporting anxiety as a continuous outcome (23-26), using a rating scale that measured anxiety but not reporting anxiety findings (27-30), reporting only patients with co-morbid anxiety and depression (31), reporting only correlational data between anxiety and another variable (32), an unpublished thesis that was not accessible (33). The total number of participants in these excluded studies is 931. An updated search run in March 2011, found three additional studies, giving a total of 44 studies in this review.

Study characteristics

Five studies were population-based and included 1,054 stroke survivors from a base population of 1,199,782. (10, 34-39) Three studies were limited to those with first ever stroke,(10, 35, 37) one excluded those with subarachnoid hemorrhage,(36) and all excluded people with major cognitive impairment, dementia or communication difficulties. Anxiety was assessed one month to five years post-stroke, and 60%-100% of eligible patients participated. The mean age of participants ranged from 66-71 years, with males representing 51%-64% of the sample (see Table 1). All studies were based on assessments from patients enrolled in a local stroke registry system.

There were 20 hospital (2, 40-58) and 14 rehabilitation based studies (59-73) which included 2,163 and 2,200 patients respectively. Allhad variable inclusion criteria (see Table 1). Additionally, there were five community-based studies (74-78) including 343 patients (see Table 1). One study accounted for 33% of the stroke participants (78). Among these three study types participation rates ranged from 31%-92%, and eight studies (43, 44, 46, 47, 57, 62, 76, 79) failed to provide information about the number of eligible stroke patients. Mean age ranged from 51-76 years with males comprising 45%-72% of the study population (see Table 1). The 44 included studies were published between 1984 and 2010 and included two studies reported in non-English language papers (xx, xx).

Measurement and assessment of anxiety

Clinical diagnoses of anxiety disorders were made in eight studies in accordance with different versions of the DSM. The DSM-III (80) was used in three studies (10, 39,

48), and three studies (34, 40, 72) used the DSM-III-R(81). The Oxfordshire Community Stroke Project (OCSP) used the DSM-III-R for its long-term follow-up so it is counted in the DSM-III, and DSM-III-R category (ref). Another three studies (45, 51, 53) used the DSM-IV (6). Eight different standardized scales were used to identify anxiety symptoms (Table 2). One study used a single question measure(69), and another used a series of five researcher developed questions to identify anxiety (74).

Anxiety Prevalence

Overall prevalence of anxiety disorders was 18% (95%CI 8%-29%, [I^2=97%, p<0.001]) (figure 1). Although the Perth Community Stroke Study (PCSS) used the DSM-III it did not apply the hierarchical diagnostic rule, so it has been included in the meta-analysis. One study (72) with an unusually low prevalence estimate contributed all of the heterogeneity of the I^2 statistic. The prevalence of anxiety disorders excluding this study is 20% (95%CI 18% - 23%, [I^2=0%, p=0.65]). Three studies,(34, 39, 51) measured different anxiety types and found that phobic disorders then GAD were the most common. One study that looked exclusively at GAD differentiated between primary GAD and GAD due to stroke. (45) It found that just over half of the anxiety cases received a primary diagnosis.

The overall frequency of anxiety 'caseness' when assessed by rating scale was 25% (95% CI 21%-28%, [I^2=90%, p<0.001]) (see Figure 1). The HADS-A was the most commonly used rating scale (see Table 2). The majority of these studies used a HADS-A cut off of 8/9 or 10/11 to define 'possible' or 'probable' anxiety. Studies using lower

cut-off on the HADS-A reported higher prevalence rates relative to those using the 'probable' threshold ([28%, 95%CI 21-35] vs [18%, 95%CI 13-23%], I^2= 79%, p=0.03). Assessment of the funnel plot (see Figure 2) revealed more asymmetry amongst studies with lower cut-off scores relative to those using the 'probable' threshold, indicating possible publication bias in favour of studies with higher prevalence estimates. *Post-hoc* analysis found no significant difference between studies that only included first-ever stroke compared to those with recurrent stroke (21% vs. 25%, respectively).

Time Course, Co-morbidity and Treatment

As the rates of anxiety reported by clinical interview and rating scales did not differ statistically, they were combined for the remaining stratified meta-analyses. There was a non-significant increase in the prevalence of anxiety over time (see Figure 3). Overall frequency was 20% (95% CI 13%-26%, [I^2= 96%, p=0.0.001]) in the acute phase; 23% (95% CI 19%-27%, [I^2= 84%, p=<0.001]) one to five months post-stroke; and 24% (95%CI 19%-29%, [I^2=89%, p=<0.001]) six months or more post-stroke. Anxiety prevalence was significantly lower in the acute phase rehabilitation-based studies relative to the other stratified subgroups, 13% (95% CI 4%-21%, I^2= 97%). Overall pooled population-based estimates (25%) did not yield significantly lower anxiety prevalence estimates than those from hospital-, rehabilitation-, or community-based populations (25% vs. 21% vs. 22%, respectively).

Three studies examined the time course of anxiety within individual stroke patients. The Collaborative Evaluation of Rehabilitation in Stroke across Europe study (63) found that 40% of patients with anxiety two months after stroke, remained anxious four months later, and 7-11% of patients not anxious at two months became so two to four months later. The population-based Perth Community Stroke Study (39) ENREF 26 found that 16% of patients with anxiety disorder at four months post-stroke, remained anxious eight months later. A similar trend was observed in a small study by Astrom (40), who reported that after three years post-stroke 62% of patients with early onset GAD had not recovered, however the small sample size from this last study mean results should be interpreted with caution.

Three studies (39, 45, 71) reported pre-stroke mood disorders and found that approximately one third of patients with post-stroke anxiety had a history of pre-stroke mood or anxiety disorder. Ten studies reported co-morbidity of anxiety and depression,(2, 39, 40, 42, 45, 51, 53, 59, 60, 70) and found that 17-80% of those with anxiety also had depression. No study reported whether stroke patients received any form of treatment for their anxiety. Additionally, two population-based studies with community-matched controls found no difference in anxiety prevalence rates between stroke and non-stroke patients (39) (10).

Clinical Correlates

Investigating anxiety was rarely a primary aim of the studies included in the review. As such, factors that might be associated with anxiety were inconsistently

reported. The variables correlated with anxiety and described in this section are those that were reported in five or more studies included in the review. There was a positive association between depression and anxiety in all six studies (45, 50, 53, 61, 67, 76) where it was assessed. Additionally 4 of 5 studies (2, 47, 56, 67, 74) found a negative correlation with quality of life. Findings were mixed for activities of daily living with 3 studies (40, 42, 45) reporting a significant negative correlation and four studies (40, 41, 51, 57) finding no association with anxiety. No association was observed with age in six of eight studies (40, 42, 45, 46, 51, 56, 59, 61); gender in five of seven (40, 45, 46, 51, 53, 59, 61); or lesion location in five of six studies (34, 40, 42, 45, 59, 65). It is likely that the probability of having anxiety after stroke is increased by having it before the stroke, but this relationship was not reported in enough studies to assess it convincingly.

Quality of evidence

Method of recruitment into studies was variable. The majority used consecutive recruitment and prevalence did not differ from those studies that used a comprehensive registry. However studies using random selection of participants tended to report higher rates. There was also variability in prevalence estimates based on the rating scales used. As many of them were used in only one study it is unclear whether this variability is due to the scale itself or some other underlying characteristic of the study population. The proportion of the eligible population was associated with prevalence. It was lowest in studies whereby 60% or more of eligible individuals participated in the study (21%). Higher prevalence was observed in studies with less than 60% of eligible individuals included (25%), and was even higher for studies whereby the proportion participating

was unclear (32%). None of the studies with longitudinal follow-up lost more than 50% of their sample at the subsequent time-point and the majority of studies provided a sufficient level of detail to characterize the study population. (Table 1)

DISCUSSION

To our knowledge this is the first published systematic review of anxiety prevalence after stroke. Anxiety disorders diagnosed by interview and anxiety symptoms assessed by rating scale occurred in approximately 20-25% of patients at any time after stroke. Phobic disorders and GAD were the most common types, however this is based on findings from only three studies. The HADS was the most used rating scales. Sensitivity for detecting anxiety disorders using the HADS-A in stroke patients using the 'probable' cut-off score ranges between 0.35 and 0.52 (82, 83), and is only marginally better when using the 'possible case' threshold. As a result the overall prevalence of significant anxiety symptoms has likely been underestimated. A recent validation study of the HADS-A in stroke patients found a score of 4 or 5 was the optimal cut-off when screening for anxiety (83). At this level the suggested requirements for psychological screening tools in stroke to have a sensitivity of >0.8 and specificity of >0.6 (84) are best met. Anxiety prevalence appears to increase somewhat over time however the increase is not statistically significant. It is possible that the lack of significance could be due to the stratified time-periods chosen *a priori*, however *post-hoc* analysis selecting different time-points also did not show a significant increase over time. With the exception of rates being lower in rehabilitation studies during the acute

phase post stroke, no significant difference was observed based on setting from which participants were recruited (e.g. population vs hospital). We hypothesize that the lower rate observed in the acute rehabilitation studies could be due to the structured supportiveenvironment, or the notion that patients deemed appropriate for rehabilitation may be less disabled and as such less likely to be anxious. Given that anxiety prevalence beyond the acute phase is the same amongst rehabilitation patients as in other groups of patients, it is perhaps indicative of a negative shift in these patients' perceptions of their rehabilitation potential and chances of returning to their pre-stroke functional level. The discrepancy in stroke sub-types, stroke severity, and variability of diagnostic tools and rating scales likely contribute to the high level of heterogeneity, and there is insufficient information to determine whether the anxiety reported was a consequence of stroke, as the majority of studies only made cross-sectional assessments and did not consider the presence of pre-stroke anxiety levels. Additionally, other factors that could impact the validity of prevalence estimates, such as medication use, the presence of cognitive or communication impairment, or previously having an anxiety disorder were not investigated.

Despite having stratified our analyses by study population and timing there was significant heterogeneity in the pooled estimates which impacts on the generalizability and interpretation of findings. Few studies differentiated between 'first-ever anxiety' and 'current anxiety' making it impossible to determine whether the differences in estimates represent genuine discrepancies or were due to measurement error or methodological differences. Second, the variation in rating scale cut-points likely contributed to

heterogeneity of pooled estimates. The review relied on studies being catalogued in major search databases and there was some evidence of small study effects such as publication bias. Additionally some studies were not included in the review as their data was unavailable and the influence this would have on the overall findings is uncertain. With the exception of the HADS and the BAI, the other scales used in these studies have not been validated in stroke populations, so their sensitivity and specificity are unknown. The HADS was most commonly used however it focuses on the psychic component of anxiety; as such anxiety-related physical symptoms not attributed to stroke are not taken into account.

CONCLUSION

This review shows that while there has been a large number of studies investigating and reporting on the frequency of anxiety after stroke, there is scant information about timing of onset, risk factors and outcomes. There also remains a lack of clarity about potential management strategies. A recent systematic review of interventions used to treat anxiety after stroke found limited evidence for use of pharmaceutical drugs (85) however other forms of treatment may be more suitable. For example, guided self-help, applied relaxation and cognitive behavioral therapy have all been shown to be effective in the general adult population (86). There is also a need to develop mood assessment tools appropriate for stroke patients with aphasia or severe communication problems, as these individuals are generally excluded from research. To date the one visual analogue mood scale found to be adequate in identifying depression post-stroke, has proved insufficient in the assessment of anxiety.

Most studies tend to examine the phenomena of anxiety and depression in isolation. However the common use of mood scales such as the HADS could facilitate an evaluation of the impact on patients of anxiety in addition to depression. There may also be differential outcomes for those with anxiety only, depression only and co-morbidity, however the design of most studies does not allow for any conclusion on this issue. Additionally, given the variability in cut-off scores used in research studies, clear guidance on the appropriate point to screen for anxiety is needed, as this would reduce, at least marginally, the heterogeneity among future studies and provide more clarity to clinical decisions about treatment. Recent large-scale surveys have reported dissatisfaction with the provision of psychological services after stroke (87). The high prevalence of anxiety in combination with a lack of available support and treatment likely contribute to this finding. Given the pervasiveness of anxiety after stroke an understanding of its impact on the patient and its economic burden, is warranted.

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DISCLOSURES

None.

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Table 1: Summary of included studies

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Oxfordshire Community Stroke Project (OCSP) 1991(10) UK	Population/ Longitudinal cohort/ All 1st ever stroke entered in registry/ Nov 1981-Oct 1986	I: 1st ever stroke (CT) E: recurrent stroke, TIA	FAST, MMSE, BDI	93% 96% 97%	71 yrs 45%	89 119 112	DSM-III (GAD)	1m 6m 1y	1.1 (0-3) 0.8 (0-3) 0
Oxfordshire Community Stroke Project (OCSP-II) 1990 (34) UK				80%	62% male	60	DSM-III-R **Anxiety (ALL)** Agoraphobia GAD Simple phobia Panic disorder	2-5y	**20(10-30)** 8.3 (1.3-15.3 5.0 (0-11) 5.0 (0-11) 2.0 (0-5)
Perth Community Stroke Study (PCSS) 1995(39) _ENREF_ 26 Australia	Population based/ Longitudinal cohort/ Ideal case finding method/ 1995-1996	I: 1st ever or recurrent stroke or TIA (WHO dfn)	Clinical variables	60%	73 yrs (56%)	294	DSM-III* **Anxiety (ALL)** Agoraphobia GAD	4m	**19 (14-23)** 16 (12-20) 3 (1-5)
South East London Stroke Study (SELSS) 1997(35) UK	Population/ Longitudinal cohort/ All strokes recorded in	I: 1st ever stroke in persons <75 including those who did not survive initial	BI, SF-36, FAI, NHP, mRS, MMSE, QoL	70%	71 yrs median (54%)	96	HADS-A≥ 8	5y	31(22-41)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
	register/ 1989-1990	event							
North East Melbourne Stroke Incidence Study (NEMSIS) 2004 (37, 38) Australia *Anxiety prevalence data unpublished	Population/ Ideal case finding method May 1996-Apr 1999	I: 1st and recurring stroke (WHO dfn, CT or MRI)	BI, LHS, NIHSS, clinical variables	Unclear	Unclear	475 498 201 424	IDA-A (score 9-15)	3m 1y 2y 5y	13 (10-16) 10 (7-13) 11 (6-15) 8.5 (6-11)
Hachiman Stroke Registration System (HSRS) 1999(36) Japan	Population/ Cohort/ All strokes entered in registry/ Jan-Dec 1987	I: All strokes	Researcher developed questionnaire covering range or clinical and social factors, Visual analog scale to measure stroke recovery	66%	66 yrs (64%)	47	GHQ-60-≥3 out of 7 on anx subscale	2.5y	43 (29-57)
Astrom, 1996 (40) Sweden	Hospital, Longitudinal cohort, Consecutive Oct 1979-Jan 1981	I: Ischemic, hemorrhagic & TIA (CT) E: Congenital mental handicap	Hemisphere lesion, ADL, Living conditions, psychosocial function, prestroke psychiatric disorder, antidepressant usage	72% 78% 83% 86% 86%	73 yrs (61%)	71 70 66 57 48	DSM-III-R(GAD)	2wk 3m 1y 2y 3y	28 (18-39) 31 (21-42) 24 (14-35) 25 (13-36) 19 (7.7-30)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Donnellan, 2010(2) Ireland	Hospital, Cross-sectional, Consecutive admissions, Not stated	I: 1st or recurrent stroke (WHO dfn, CT) & FAST ≥14, & AMT ≥8 E: TIA, SAH, traumatic intracranial haemorrhage, dementia, extreme critical illness	Marital status, living arrangements, SES, ADL, NEADL, SSQOL	53%	Range 20-98 yrs (51%)	107 107	HADS-A≥8	1m 1y	33 (24-42) 32 (23-41)
Field, 2008(41) UK	Hospital/ Cross-sectional/ Nurse approached all patients meeting inclusion criteria/ Year not stated	E: Cognitive impairment, aphasia, acute medical problems	PTCI, PDS	89%	72 yrs (53%)	81	HADS-A≥11	<1m	21 (12-30)
Fure, 2006(42) Norway	Hospital, Cross-sectional, Consecutive enrolment, Dec 2000-Jan 2002	I: Stroke (CT) E: TIA, moderate to severe aphasia, consciousness	NIHSS, BI, MMSE, MRS	64%	69 yrs (63%)	178	HADS-A≥8	1wk	26 (20-33)
Ibrahimagic, 2005(43)	Hospital,	I: Ischemic		Not stated	65 yrs (50%	40	Zung≥50	2 days	30 (16-44)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Bosnia	Prospective longitudinal cohort/ Consecutive enrolment/ Year not state	stroke (CT) and able to fill out self report questionnaire			male)	40		2wk	25 (12-38)
Knapp, 1998(44) UK	Hospital/ Cross-sectional/ Consecutive enrolment/ Year not stated	I: Stroke within past month, sufficient language and cognition to undertake long interview, named carer also willing to participate, living independently pre-stroke	BI, Schedule for Social interaction	Not stated	69 yrs (53%)	30 30 30	HADS-A≥8	<1m 1m post discharge 6m post discharge	47 (29-65) 27 (11-43) 30 (14-47)
Leppavuori, 2003(45) Finland ENREF 40	Hospital/ Cross-sectional cohort/ consecutive enrolment/ Not stated	I: Ischemic stroke (MRI) E: SAH, ICH, no clinical neurological examination, severe apasia, refusal of psychiatric examination	BI, MMSE, SSS, Zung anxiety scale, Global Assessment of Functioning, MADRS	57%	71 yrs (51%)	277	DSM-IV_GAD	3-4m	21 (16-26)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Li, 2006(46) China_ENREF_63	Hospital/ Cross-sectional/ Random selection/ 2000-2002	I: Cerebral infarction		Not stated	53 yrs (53%)	91	HADS-A>9	Not reported	31 (21-40)
Merriman 2007(58) UK	Hospital/ Cross-sectional/ In-hospital and postal-mailout to discharged patients/ Year not stated	I: ≥18 yrs & 1-12 months post stroke, able to complete self-report questionnaire E: Dysphasia, acute medical problems	PDS, BI, Negative Affect Schedule, Cognitive Appraisal Questionnaire	52%	74 yrs (56%)	102	HADS-A≥11	1-12m	20 (12-27)
Moon, 2004(47), South Korea	Hospital/ Cross-sectional/ Consecutive enrolment/ Feb- Jun 2002	I: Stroke (MRI)	BDI, BI, WHOQOL-BREF	Not reported	Mean age unknown (62%)	69	BAI≥22	2m	49 (37-61)
Morris, 1990(48), Australia	Hospital/ Longitudinal cohort/ Consecutive enrolment	I:Ischemic & Hemorrhagic (WHO DFN, CT) E: Aphasia, however two individuals with minimal deficit included	BI, Social class, MMSE, Family psychiatric history, MADRS	Not reported	71 yrs (51%)	99	DSM-III	2m	3.0 (0-6.4)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
						56		1y	5.4 (0-11)
Morrison 2000 & 2005(49, 50) UK	Hospital/ Longitudinal cohort/ Recruitment over 13 months for patients admitted to hospital/ Year not stated	I: residual disability, pass screening test for cognitive and communication problems	BI, RLOC, CAPE, Exercise coping, Recovery confidence, Neurologic impairment	89% 89% 93% 86$	69 yrs (51%)	101 78 71 38	HADS-A≥11	<1m 2m 6m 3y	24 (15-32) 21 (12-29) 23 (13-32) 26 (12-40)
Raju, 2010(56) India	Hospital/ Cross-sectional/ Patients who had completed ≥1 month follow-up/ Nov 2008-Feb 2010	I: 1st ever Ischemic & Hemorrhagic stroke (WHO dfn, CT or MRI), ≥1 month post-stroke E: history of psychoactive substance abuse, dementia, psychiatric co-morbidity, aphasia	FIM, WHOQoL-BREF, NIHSS, mRS	81%	54 yrs (70%)	162	HADS-A≥11	1.5y	11 (6.3-16)
Sagen, 2010(51) Norway	Hospital/ Cross-sectional/	I: Ischemic or hemorrhagic	AES, BI, SSS, HADS	57%	65 yrs (59%)	104	DSM-IV **Anxiety (ALL)**	4m	**23 (15-31)**

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
	Consecutive enrolment/ Jan 2003-Jun 2005	stroke E: TIA, aphasia, psychosis, MMSE <20, terminal illness					GAD PTSD Social phobia Panic with Ag. Panic without Ag. Agoraphobia without Panic OCD Anxiety NOS		5.8 (1.3-10) 2.9 (0-6.1) 2.9 (0-6.1) 7.7 (2.6-13) 2.9 (0-6.1) 3.9 (0-7.5) 1.9 (0-4.6) 1.0 (0-2.8)
Sampson, 2003(52) UK	Hospital/ Case-control/ Recruit from 6 stroke units/ Year not stated	I: Ischemic or hemorrhagic stroke E: Cognitive impairment, dysphasia, too physically unwell or terminal illness, MRSA infection	BI, GHQ-28, IES, PCL-S, MMSE, Verbal Fluency Test, Digit Span Test, National Adult Reading Test	69%	Not reported	54	HADS-A≥10	Not reported	26 (14-38)
Schultz, 1997(53) USA	Hospital/ Longitudinal cohort/ Consecutive enrolment/ Year unclear	I: Stroke	HAM-D, MMSE, STC, JHFI	Unclear	58 yrs (57%)	142 77 79 70 66	DSM-IV_GAD	Acute phase 3m 6m 12m 2y	19 (13-25) 22 (13-31) 25 (16-35) 11 (4.0-19) 18 (8.9-27)
Stone, 2004(54) UK	Hospital/ Nested cross-sectional/	E: Severe stroke with high risk of death,	NEADL, carer distress	71%	72 yrs median (60%)	89	HADS-A≥8	1m	20 (12-29)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
	Consecutive enrolment/ Year not stated	dementia, aphasia, cognitive impairment, patients living alone, carer unable to talk with researcher							
Townend, 2007(55) Australia	Hospital/ Longitudinal cohort/ Consecutive enrolment/ Mar-Sep 2004	I: Ischemic or hemorrhagic stroke E: Dysphagia, MMSE<20, reduced level of consciousness	BI, mRS, MMSE, Social support scale	83%	76 yrs (49%)	125	HADS-A≥9	5 days	4.8 (1.1-8.6)
				95%		112		1m	8.0 (3.0-13)
				92%		105		3m	14 (7.6-21)
Wanatabe, 1984(79) Japan_ENREF_65	Hospital/ Cross-Sectional/ Random selection/ Year not stated	E: aphasia, dementia	Clinical factors	Not reported	57 yrs (57%)	35	TMAS	6m	51 (35-68)
Zhao, 1999(57) China	Hospital	I: 1st ever stroke (Chinese Cerebral Vascular Disease Symposium of	Clinical factors	Not reported	63 yrs (61%)	206	Zung SAS≥50	1m	18 (13-24)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
		1995 Dfn) E: Aphasia, -mental disorder, epilepsy, mental retardation, cerebral trauma							
Barker-Collo, 2007(59) New Zealand	Rehabilitation, Cross-Sectional Consecutive, Not stated	I: Ischemic, Hemorrhagic (CT) E: Aphasia, non-native language speaker	Education, Marital Status, BDI, FIM, Verbal learning, Memory, Impulse control	81%	52 yrs (55%)	73	BAI≥26	3m	21 (11-32)
Bergersen, 2010(60) Norway	Rehabilitation, Cross-Sectional, Mail-out all patients 1998-2001	I: Ischemic, ICH, SAH E: Aphasia	Marital status, Employment, Driver's license, Family support, MRS, GHQ-30	64%	58 yrs (64%)	162	HADS-A≥11	2-5y	17 (11-22)
Carod-Artal 2009(61) Brazil	Rehabilitation, Cross-sectional, Consecutive, Jul 2007-Jun	I: Ischemic & hemorrhagic (Clinical dx and radiological	NIHSS, MRS, BI, MMSE, Lawton & Brody Scale (extended ADL), SIS	77%	56 yrs (52%)	300	HADS-A≥11	20m	24 (19-29)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
	2008	findings) E: TIA, subdural haematoma, dementia, aphasia, severe disability due to previous neurological disorder							
D'Alisa 2005(62) Italy	Rehabilitation, Cross-sectional, Consecutive, Not stated	E:MMSE <24, Aphasia	MMSE, FIM, LHS, UNSS	unclear	63 yrs (60%)	73	HADS-A≥11	5y	21 (11-30)
DeWit 2008(63) England, Belgium, Switzerland, Germany	Rehabilitation, Longitudinal cohort, Consecutive	I: 1st ever stroke (WHO criteria-CT), RMA-GF≤11 and/or Leg Trunk function ≤8 and/or Arm function ≤12 E: neurological impairments, pre-stroke BI<50, subdural hematoma, admitted to rehab centre ≥6 wks post-stroke	BI, NIHSS, RMA-GF	95% 95% 92%	70 yrs (53%)	491 478 467	HADS-A≥8	2m 4m 6m	25 (21-29) 23 (19-27) 21 (18-25)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Gangstad 2009(64) UK	Rehabilitation/ Cross-sectional/ All patients attending clinic approached meeting inclusion approached/ Study conducted over 6 months	E: Cognitive impairment	Cognitive Processing of Trauma Scale, Posttraumatic Growth Inventory	100%	Not provided	15	HADS-A≥11	14m	6.7 (0-19)
Ghika-Schmid 1999(65) Switzerland	Rehabilitation/ Cross-sectional/ Consecutive enrolment/ Year not stated	I: 1st ever stroke only (CT or MRI)	BI, MRS, HDRS	72%	60 yrs (not provided)	31	HAM-A>14	3m	29 (13-45)
Giaquinto 2007(66) Italy	Rehabilitation/ Consecutive enrolment/	I: 1st ever stroke only (CT or MRI) E: TIA, SAH, previous stroke but not TIA, admission to rehab>3 weeks post-stroke, severe co-morbidity, mental or comprehension impairment	MMSE, FIM, Royal Free Interview, Cumulative Illness Rating Scale	81%	70 yrs (46%)	132	HADS-A≥6	10 days	42 (33-50)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Masskulpan & Kuptniratsaikul 2008(67, 68) Thailand	Rehabilitation/ Prospective longitudinal cohort/ National registry from consecutive enrolled patients/ Mar-Dec 2006	I: Stroke patients ≥18 yrs E: Severe medical comorbidities, Inability to communicate, dementia, schizophrenia or present psychotic episode	BI, MMSE, WHOQOL-BREF	Not stated 77%	62 yrs (59%)	327 251	HADS-A≥11	~24 days 2m	5.8 (3.3-8.4) 26 (20-31)
Langhorne 2000(69) UK	Rehabilitation/ Prospective longitudinal cohort/ Multi-centre consecutive enrolment/ 7 months	I: Stroke (WHO dfn) within 7 days of onset	BI, FIM, Clinical complications	71% 82% 86%	76 yrs (52%)	220 181 155	Single Question	6m post discharge 18m post discharge 30m post discharge	34 (28-40) 44 (37-51) 49 (41-57)
Macniven 2005(70) UK	Rehabilitation/ Cross-sectional/ 2 week audit of all patients on ward/ Year not stated	E: Language problems	Tests for memory, reasoning, language, executive functioning, praxis & visuospatial-perceptual functioning	57%	68 yrs (47%)	17	HADS-A≥8	58.5 days	65 (42-87)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Sembi 1998(71) UK	Rehabilitation/ Cross-sectional/ Recruited from 3 rehab sites/ Jan 1995-Apr 1996	I: >18 yrs with 1st ever stroke or TIA, able to complete self-report questionnaire E: Dysphasia	BI, EPQ, GHQ-28, IES, Penn	77%	66 yrs (% male not reported)	61	HADS-A≥11	18m	15 (5.9-24)
Tang 2002(72) Hong Kong	Rehabilitation/ Cross-sectional/ Consecutive enrolment/ Jun 1999-Aug 2000	I: 1st ever stroke (CT) E: TIA, SAH, history of neurological impairment, comprehension and communication deficits, length of stay <2 wks	BI, MMSE, mRS, NIHSS	31%	71 yrs (45%)	157	DSM-III-R	25 days	0.6 (0-1.9)
Vickery 2006(73) USA	Rehabilitation/ Cross-sectional/ Sample of admitted patients/ Year not stated	I: Stroke E: history of co-morbid dementia, non-stroke neurological process, acute delirium, severe psychiatric disturbance	VASES, GDS, VAMS	90%	69 yrs (45%)	141	AMAS ≥65	20 days	7.8 (3.4-12)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
Ahlsio, 1984(74) Sweden	Community Cross-Sectional, Consecutive, Jan-Dec 1979	I: CI, TIA, SAH (CT) E: Severe disability, aphasia, dementia	ADL, QoL, mortality	55%	71 yrs, (60%)	53	Self Report	2y	26 (15-38)
Bruggiman, 2006(75) Switzerland	Community, Cross-sectional, consecutive, Not stated	I: 1st ever Ischemic or Hemorrhagic stroke E: NIHSS>3, history of psychiatric illness, neurologic comorbidity	MRI, BI, HDRS, NIHSS, Memory assessment, IES, Trauma experience	52%	51 yrs (67%)	49	HADS-A≥8	1y	24 (12-37)
Gillespie, 1997(76) UK	Community/ Cross-sectional/ Registry mailout to discharged patients/ Year not stated	I: Stroke (WHO dfn) E: Communication difficulties, cognitive impairment, significant comorbidity, recent	BI, Coping checklist	68%	69 yrs (66%)	44	HADS-A≥9	7m	25 (12-38)

Study name or author, year published Location	Setting/ Design/ Recruitment/ Year of study	Inclusion (I)/ exclusion (E)	Other Measures administered	% Eligible participating	Mean age (%male)/	N	Criteria	Time Post Stroke	Percent wit Anxiety (95 CI)
		experience of major life event unrelated to stroke							
Lincoln, 1998(77) UK	Community/ Cross-sectional/ 74 GP practices/ Aug 1994-Aug 1996	I: Stroke (WHO dfn)	BI, cognitive ability, Rivermead Motor Assessment, London Handicap Scale	82%	76 yrs (67%)	84	HADS-A≥11	1m	26 (17-36)
Visser-Keizer, 2002(78) Netherlands	Community/ Cross-sectional/ 350 GP clinics/ Year not stated	I: 1st ever ischemic stroke (CT) E: neurologic or psychiatric history, history of alcohol or drug abuse, insufficient language and cognitive ability to allow assessment, aphasia	BI, verbal memory, hemispatial neglect	61%	67 yrs (59%)	113	HADS-A≥6	3m	14 (7.7-21)

AES: Apathy Evaluation Scale, **AMAS**: Adult Manifest Anxiety Scale, **AMT**: Abbreviated Mental Test, **BAI**: Beck Anxiety Inventory, **BI:** Barthel Index **CI:** Cerebral Infarction, **DSM**: Diagnostic and Statistical Manual of Mental Disorders, **EPQ:** Eysenck Personality Questionnaire, **FAI:** Frenchay's Activity Index, , **FAST:** Frenchay Aphasia Screening Test , **GDS:** Geriatric Depression Scale, **GHQ**: General Health Questionnaire, **HADS-A**: Hospital Anxiety and Depression Scale Anxiety Subscale, **HAM-A:** Hamilton Anxiety Scale, **HDRS:** Hamilton Depression Rating Scale, **ICH:** Intracerebral Hemorrhage, **IDA-A**: Irritability Depression and Anxiety Scale, Anxiety subscale, **IES**: Impact of Event Scale **JHFI:** Johns Hopkins Functioning Inventory, **LHS**: London Handicap Scale, **MADRS:** Montgomery-Asberg Depression Scale, **MMSE:** Mini Mental State Examination, **MRI:** Magnetic Resonance Imaging, **MRS:** Modified Rankin Score, **NHP:** Nottingham Health Profile, **NIHSS**: National Institute of Health Stroke

Scale, **PDS:** Posttraumatic Diagnostic Scale, **Penn:** Penn Inventory of PTSD, **PTCI**: Posttraumatic Cognitions Inventory, **RMA-GF**: Rivermead Motor Assessment, **SAH:** Subarachnoid Hemorrhage, **SF-36**: Short Form-36, **SIS**: Stroke Impact Scale, **SSS:** Scandinavian Stroke Scale, **STC:** Social Ties Checklist, **TIA:** Transient Ischemic Attack, **TMAS**: Taylor Manifest Anxiety Scale, **UNSS:** Unified Neurological Stroke Scale, **VAMS:** Visual Analog Mood Scales, **VASES**: Visual Analogue Self-Esteem Scale, **Zung SAS**: Zung Self Rating Anxiety Scale

Table 2: Synopsis of rating scales used to measure anxiety symptoms

Screening tool	Details	No. studies	Suggested threshold scoring	Cut-off scores reported from studies
Adult Manifest Anxiety Scale (AMAS)(88)	Self report scale with 36 to 44 items. Total number of anxiety items endorsed is summed and converted to an age-referenced T-score	1	Age dependent	T-score ≥65
Beck Anxiety Inventory (BAI)(89)	Self-report 21 item scale that discriminates between anxiety and depression. Possible score ranges from 0-63.	2	0-7 minimal 8-15 mild 16-25 moderate 26-63 severe anxiety	≥16, >22
General Health Questionnaire-60 (GHQ-60)(90)	A 60 item scale used to screen for various aspects of psychiatric distress. Includes an anxiety subscale.	1	Determined by researcher	≥3 out of 7 on anxiety subscale
Hamilton Anxiety Rating Scale (HAM-A)(91)	Clinician administered 14 item scale measuring specific anxiety symptom clusters that are both psychic and somatic. Possible score ranges from 0-56	1	<17 mild 18-24 mild to moderate ≥25 severe anxiety	>14
Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A)(92)	Self-report 14 item scale with 7 items used to screen for psychic anxiety symptoms. Possible score ranges from 0-21.	25	0-7 minimal 8/9 possible anxiety disorder 10/11 probable anxiety disorder.	≥6, ≥8, >8, ≥9, ≥10, ≥11
Irritability Depression and Anxiety, Anxiety subscale (IDA-A)(93)	Self report scale with 5 items anxiety subscale. Possible scores range from 0-15	1	0-8 minimal to mild 9-15 moderate to severe anxiety	≥9
Taylor Manifest Anxiety Scale (TMAS)(94)	Clinician administered 50 item scale. Possible scores range from 0-50 with higher score indicative of higher levels of trait anxiety.	1	14/15 indicative of anxiety, differential sex based thresholds recommended	>23 for males, >26 females
Zung Self Rating Anxiety Scale(95)	Self report 20 item scale with measures of state and trait anxiety. Possible scores range from 20-80	2	20-44 normal 45-59 mild to moderate 60-74 severe 75-80 extreme anxiety	≥50