Self Report Questionnaire Assessment of Anxiety and Depression amongst Stroke Patients in Rehabilitation Settings

And Clinical Research Portfolio

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Chapter 1

Systematic Review

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Abstract

Background and Purpose: There is a growing body of evidence around depression as a risk factor for incident stroke. This literature has been reviewed previously, but not subjected to a full systematic review. In particular, many recent papers have not been reviewed. This paper aims to provide a clear overview of the research on depression as risk factor for stroke, and suggestions for future research.

Methods: The relevant literature was systematically collated and then reviewed using selected criteria within a categorised structure.

Results: 21 relevant studies were identified. All studies found depression to raise the risk of subsequent stroke. This effect remained when several other known risk factors were adjusted for. However, the quality of the studies was variable.

Conclusions: Depression was found to be a risk factor for stroke. The scale of this effect is unclear but may be of the same order as that associated with smoking. Further research to clarify effect size and mechanisms is required.

Key Words: Depression, Stroke, Risk Factor, Systematic Review

Introduction

Stroke is a medical condition caused by the disruption of oxygenated blood supply to one or more brain areas, the detrimental effects of which can be physical, emotional and cognitive [1]. By definition these effects last more than 24 hours to disambiguate stroke from Transient Ischaemic Attack [TIA]. The degree of recovery varies.

The World Health Organisation [WHO] also describes the high economic cost of stroke for many countries. Stroke is described as responsible for "3% of total health care costs in the Netherlands in 1994". For the UK, the estimated share of the health care budget taken by stroke in 2000 was 4% [2]. Globally, WHO attributes 5 million deaths and 5 million cases of severe disability to stroke each year[3].

The Scottish Government's "Better Heart Disease and Stroke Care Action Plan" [2009] [4]explores recent mortality rates in more detail, noting an overall fall in stroke mortality for Scots over 75 years old. However the absolute number of people suffering stroke is likely to increase as the population ages "if the age specific incidence is not reduced by primary prevention". Possible increases due to rates of obesity, diabetes and alcohol misuse are also noted. This flags up the potential gap between identification of risk factors and effective moderation of them.

There is a well established link between stroke and subsequent depressive illness [5] and depressive illness as a mediating factor in poorer outcomes following stroke [6 7]. As such, routine screening for mood disorder following stroke as a first step towards effective rehabilitation is indicated in guidelines from the Royal College of Physicians [RCP] and Scottish Intercollegiate Guidelines Network [SIGN][8,9]. There is also now a growing body of research into depressive illness as a risk factor for incident stroke [10]. This is of clinical interest as depression is both common and treatable.

Various direct and indirect mechanisms for depression to influence risk of stroke have been proposed. These include poor health behaviours [1112], non-optimal regulation of blood pressure and inflammatory processes [13]

Other research has focussed on the possibility that cerebro-vascular changes in older adults can induce a low mood state that has distinctive clinical features. These include limited insight to one's own affect and resistance to orthodox treatments for depression. This is known as the "vascular depression hypothesis" [14,15] The validity of this hypothesis remains uncertain, with a recent systematic review [15] finding insufficient evidence to endorse it. However, the vascular depression hypothesis does provide another mechanism model, with cerebro-vascular change underlying both incipient depression and subsequent stroke. In terms of intervention then, treatment of the vascular condition rather than the depression might be indicated [16,17]

From a clinical perspective, the mechanisms involved might be considered as of secondary interest. The key question of relevance for clinical purposes is whether depression does indeed increase the risk of subsequent stroke, and in what degree. This would enable more accurate assessment of overall risk, in combination with other factors. From a research perspective, if depression does appear to be a significant risk factor for subsequent stroke then other questions arise. For example, it would be useful to know more about underlying mechanisms and to assess the extent to which pre-stroke depression maps onto post-stroke depression and hence poorer outcomes.

This paper aims to provide a systematic review of research into depression as a risk factor for stroke using criteria adapted from the 49 threats to validity collated and discussed by Cook [18] and Ellis [19]. These are described in more detail in the Methods section, as is the overall review process.

Methods

Firstly, the existence of systematic reviews in this area was explored. An advanced search of the Cochrane Database of Systematic Reviews was conducted using the search terms “depression”, “risk factor” and “stroke”. No papers regarding depression as a risk factor for stroke were identified in this search. This was supplemented by a Google Scholar search. Again, no systematic reviews of depression as a risk factor for stroke were identified.

Therefore a fuller multi-database literature search of Journals @ Ovid Full Text, Ovid MEDLINE(R) [1996-present],Embase [1996-present] , CINAHL, PsycARTICLES, Psychology and Behavioral Sciences Collection and PsycINFO was conducted for papers concerning depression as a risk factor for stroke. The search terms were “ Depression/ or cyclothymia/ or atypical depression/ or endogenous depression/ or involutional depression/ or major depression”, “Cerebrovascular accident/ or stroke/ or CVA” and "Danger, risk, safety and related phenomena"/ or health hazard/ or high risk population/ or morbidity/ or population risk”
Where possible search filters for adult population (18+) and Literature Reviews were applied.
The results of these searches were combined using the Boolean operator “AND”. Duplicates were removed from the resultant tranche of papers using an automated “de-duplicate” process.
These combined searches yielded 461 items which were then individually checked for relevance.

The research literature yielded by this search will be discussed more fully in the Results and Discussion sections. However, the literature search also found three reviews, of varying methodology, that in some way addressed the question central to this review.

Wulsin et al. [20]published a systematic review of papers which addressed depression as a cause of mortality extant in “all relevant English language databases from 1966 to 1996”.

Ramasubbu [21] provided a narrative review of 8 studies exploring depression as a risk factor for stroke morbidity and/or mortality, which they based on searching Medline articles in English from January 1966 to December 2001.

Van der Kooy [22] carried out a systematic review and meta-analysis of 28 papers from "MEDLINE (1966–2005) and PSYCHINFO (1966–2005)" that explored depression as a risk factor for a range of vascular conditions. Of these 28 papers, 10 explicitly address depression as a risk factor for stroke. Of these 10, only 5 are assessed by Van der Kooy et al. as being of "high quality"[22].

Wulsin et al. report, cautiously, that depression increases mortality and identify cardio-vascular disease as particularly associated with depression. However, they do not clearly address stroke as a separate vascular condition and focus on mortality rather than condition incidence[20].
Ramasubbu et al. discuss methodological aspects of the papers they review but do not provide a systematic review. Their overall conclusion is couched cautiously, describing the literature as "emerging" and stating the need for further studies[21].
Van der Kooy et al. do provide a systematic review of paper quality, which is used to inform their meta-analysis of effect size[22]. However, there have been several papers published in this area after 2005 [13], [23], [24]. In short, there is no up to date systematic review of evidence for depression as a stroke risk factor.

The search protocol yielded many studies that explored the connection between depressive symptoms and vascular events. From the perspective of the present review many of these took too broad a view of vascular events comprising both cardio- and cerebro-vascular events, as well as broader vascular function without differentiating etiologies. Alternatively, some focussed on a single aspect of vascular function that did not address the question driving this review; for example,

focussing on cardio-vascular health. Such studies were discarded at this stage. This yielded 29 papers which addressed the broad area of depression as a risk factor for stroke. Checking the references of these papers yielded a further 5 papers. This new total of 34 papers was further winnowed using the following criteria: Explicit use of the terms “depression” or “depressive” and “stroke” within the paper, clearly addressing depressive symptoms as a risk factor for stroke (rather than a consequence, use of a methodical approach to test the hypothesis that depression is a risk factor for stroke (i.e. not solely a discussion paper).

This left 20 papers that clearly addressed the review question “Is depression a risk factor for incident stroke”. Most commonly the surviving papers employed prospective follow-up of outcomes for large samples (multiple 1000’s) that had undergone some form of baseline screening or assessment.

The fundamental assessment of the studies was conducted using 32 criteria adapted from the 49 threats to validity originally outlined by Cook [18] and further discussed by Ellis [19]. In order to provide clear information about study quality it was decided to apply these criteria dichotomously, rather than grading the extent to which they were met. In order to provide a more nuanced but still accessible summary of the aggregate score it was decided to use a range of sub-scores. SIGN 50 outlines a categorisation system that can be applied to reviews[25]. This is the “PICO” format, an acronym comprising 4 areas – Population, Intervention, Comparison and Outcomes.

For the purposes of the present review the PICO format offered useful categories in a suitably accessible way. However, as the types of study considered in this review differ somewhat from the Randomised Controlled Trials which the PICO format was created for, their present use is clarified by a brief overview of the 4 categories and explication of how the selected criteria are applied within them.

PICO format and criteria used

Population

The population group in this review is primarily defined by sample selection, management and reporting. The main aim is to ensure that studies have managed sources of bias and have maximised generalisability. The criteria in this category address several aspects related to population: explicit inclusion and exclusion criteria, report and accounting of participant attrition, sample selection and demographic reporting.

Intervention

In the context of the present review "Intervention" is effectively "Risk Factor". To be more specific, the mediating condition of interest is depressive illness. The focus of the criteria in this category is to ensure that depression is robustly defined and measured. The specific criteria in this category explore the definition and measures of depression (e.g. to DSM or ICD criteria), and the assessment of depressive chronicity.

Comparison

This category looks at the quality of contextual assessment of the index condition. This includes consideration of models underlying the study methodology and other known risk factors for stroke. The specific criteria in this category explore the presence of models or interventions, study design and focus on the risk-factor(s). In particular, this category explores the accounting for established risk factors such as age, stroke history, hypertension, atrial fibrillation and heart disease, cigarette use, diabetes, obesity, high blood cholesterol, arterial disease and sickle cell anaemia.

Outcomes

For the present study the outcome of interest is incident stroke. Therefore the focus of the criteria is how robustly stroke is defined and assessed, and the appropriateness of statistical analyses. The specific criteria in this category explore the clarity of study focus on stroke, stroke definition and diagnosis. It also considers the appropriateness of the statistics used.

With regard to statistical power, an initial statistical exploration was undertaken. All studies were found to be adequately powered for their effect size, assuming a maximum p-value of 0.05 and a minimum statistical power of 0.8. This reflected large sample sizes in most of the studies.

An independent person used these criteria to assess an initial random selection of 4 of the 20 surviving studies. This was done simultaneously with the researcher to establish inter-rater reliability through easy cross checking of criteria use. The discrepancy rate between overall scores varied from 3% to 10%. The points of variance were not concentrated on any one factor or PICO category and were discussed and rectified without difficulty. A further 4 papers were then double marked separately. For three of these, the discrepancy rate between markers overall was zero. The discrepancy rate for the fourth was 7%. Therefore, the review criteria appear to be clear in their application.

Results

To initially summarise the review findings, all but one study found that depression was to some extent a risk factor for stroke. Overall PICO scores ranged from 12 to 26 of a possible 32. Fifteen studies scored 20 or over, meaning they had met at least 62.5% of quality criteria. It is also preferable that papers perform adequately across all PICO categories, meeting at least half the criteria. As indicated by the PICO categories there are at least 4 components that determine the

usefulness of the studies. These can be summarised as 1) a study population that lends itself to generalising the results 2) a robust definition of depression 3) robust assessment of other known risk factors for stroke and 4) a robust definition of stroke. Key individual factors may also strongly affect the quality of the paper as a whole. There may be a confirmation bias in studies that achieve publication, and the present review is limited to those studies published in English.

The studies all report 95% Confidence Intervals for their main findings, typically expressed as Hazard Ratios. Hazard Ratios represent multipliers for baseline risk. Therefore a Hazard Ratio of 1 represents "no effect". In the context of the present review, a Hazard Ratio value below 1 indicates a reduction in baseline risk of stroke. Although a precise p-value cannot be inferred from a Confidence Interval it is possible to infer statistical significance. In the case of 95% Confidence Intervals this would be at the 0.05 level reflecting the 5% (0.05) of potential variation not accounted for in the statistic. Statistical significance may be inferred if the value indicating "no effect" (in this case a value of 1) is not within the stated Confidence Intervals.

Eight of the studies in this review do not directly report statistical significance for their main findings. Of these, five can be inferred from their Confidence Intervals to have attained statistical significance at the 0.05 level. Three can be inferred not to have attained statistical significance at the 0.05 level. Ten of the twelve studies which do report p-values attain statistical significance at the 0.05 level for their main finding.

All of the studies but two (Nilsson et al. and Lee et al.) employ a prospective and longitudinal methodology, following up relatively large samples after baseline assessment to ascertain risk of incident stroke. This often taps into cohorts engaged in established epidemiological studies. The approach used by Nilsson et al. and Lee et al. is distinct in collating their data from administrative

and medical records, rather than direct researcher interaction with participants, but is otherwise very similar to the other studies reviewed. Where studies do differ is in terms of the participant age at entry to the study.

Difference in participant age at point of entry into the studies reviewed is a matter of clinical interest. The average age at which first stroke occurs in developed countries is 73 years old, making this group the most likely to be seen by clinicians[52]. It is also of relevance to public health as this is the age cohort which place highest demand on stroke services[2], and which might benefit most from effective intervention.

Eight of the studies recruited participants between the ages of 55 and 65 at entry. As these studies are prospective, with follow-up ranging from 6-11 years, the cohorts they follow are broadly age "typical" for first onset stroke. A further group of seven studies recruited participants from a much wider age range (18 to 70+ at entry to study). Although these cohorts do include participants in the age range most likely to have a stroke during study, they also include participants from outlying age ranges which are "atypical for first stroke." This may skew their findings. A further two studies focussed recruitment on participants from very atypical age ranges in relation to incidence of first stroke (18-44 years and over 85 years). Three of the studies are also distinct in terms of their samples in only recruiting participants of a single gender, so these are considered separately.

Age at entry to study typical for first onset stroke

Simons et al. followed participants aged 60+ for c. 8years (follow-up was ongoing at the time their paper was written) [38]**.** This study did not report definition and measurement of depression clearly, but performed adequately across other PICO categories. Depression was found to be a risk factor for stroke but was not clearly differentiated from other risk factors.

Bos et al. followed participants aged at least 61 for a minimum of 6 years [24]. The study performed well across all PICO categories and its analyses differentiated between genders and levels of depression. Depressive symptoms, but not DSM-IV defined Depressive Disorder, were found to be a stroke risk factor for men only.

Colantonio et al. followed participants aged 65+ from an established longitudinal health study over a 6 year period [26]. This gave the researchers quite detailed collateral information about potential mediators of stroke risk not commonly addressed in the reviewed studies. For example, religious observance, marital status and level of social support were all found to be somewhat protective factors. In terms of the present review, depression was found to be a risk factor for stroke when considered in isolation. However the effects of all the noted protective and risk factors were not retained when health variables were adjusted for. This was the only study which did not find depression to be an overall risk factor for stroke. Its performance across PICO categories was adequate.

Arbelaez et al. followed participants aged 65+ for 11 years [13]**.** This study was somewhat unusual in exploring a potential mechanism (inflammation). Although the potential mediating role of inflammation was not supported, depression was found to be risk factor for ischaemic stroke. As might be expected medical outcomes were well operationalised in this study. However depression was less clearly defined and assessed.

Ostir et al. followed participants aged 65+ for 6 years [36] in a study that performed adequately across PICO criteria. Their focus was on the role of emotional well-being on stroke incidence, so as well as depression they also measured “positive affect”. This was achieved by reverse scoring and factor

analysis of the Center for Epidemiological Studies Depression Scale, which had been used in the normal way to assess depression. They found that depression was a risk factor for stroke, but also that high levels of "positive affect" were protective, compared to baseline incidence.

Simonsick et al. drew a sample of participants aged 65+ from an established epidemiological study, and followed them for 6 years[12]. They had a particular interest in the role of hypertension plus depression in subsequent stroke. Hypertension was well measured but depression was assessed using multiple adaptations of the Center for Epidemiological Studies Depression Scale and dichotomised into "high" and "low" symptom endorsement. The rationale and evidence base for this was not clear. Similarly, stroke categorisation was based on participant self-report of diagnosis. "High" endorsement of depressive symptoms was found to be a risk factor for stroke.

Wouts et al. describe their cohort of people aged 55+ as "elderly", which may be more in keeping with the mean participant age of 70.5 (SD 8.7) [41]. This study has a focus on cardiac disease as a potential mediating influence. It performed adequately across PICO categories and found "Clinically Relevant Depressive Symptoms" in combination with pre-existing cardiac disease to be a risk factor for stroke.

Whooley et al. do not make their age cut-offs explicit, but report a mean participant age of 63 (SD 12) which corresponds reasonably well with the other papers within this group [40]. This paper performs adequately across PICO categories and has a focus on health behaviours as potential mediators of the relationship between depression and subsequent stroke. Depression is individually found to be a risk factor for stroke. However, this association is greatly reduced and becomes statistically non-significant when other factors, in particular health behaviours, are accounted for.

To summarise this group of papers, all but one[26] found depression to be a risk factor for stroke. However, of the seven papers supporting depression as a risk factor one[12] was of lower quality, one[41] only found this only in combination with pre-existent cardiac disease and one[40] found this association to be highly attenuated by co-morbidity and health behaviours. The effect sizes were also relatively modest, with Hazard Ratios for the four papers which most clearly say depression is a risk factor for stroke[38 24 13 36] ranging from 1.04 to 1.41.

Age at entry to study includes participants atypical of first onset stroke

Everson et al. studied a sample aged 17-94 at entry to study, who were part of an existing epidemiological study[27]. This allowed follow-up data over 29 years to be used. However, the authors acknowledge limitations with the depression measure used, and that it does not fully address standard diagnostic criteria. The study performed well across other PICO categories and found that depression was a risk factor for stroke.

Larson et al. drew on a sample of participants aged 18 to 65+ who were already engaged with large scale epidemiological study[30]. Follow up was for 13 years, and depression was notably well defined and assessed in this study, taking DSM criteria Depressive Disorder as an index. However, other risk factors were less well accounted for. This study did find depression to be a risk factor for stroke across the whole sample, noting an increase in effect with aging, particularly beyond 45 years old.

Jonas et al. studied a sample aged 25-74 at entry to study, who were followed for an average of 16 years[29]. This study performed adequately across PICO categories. An interesting feature of this study is that it also categorised participants by race (“Black” or “White”). The basis for this categorisation is not made explicit, but it is noted that “other races” were not included due to small numbers.

Depression was found to be a risk factor for stroke across the whole sample, but the effect was larger for those participants categorised as “Black”.

Salaycik et al. tapped into a long-established epidemiological study, gathering data on participants aged from 29-100 at entry for an 8 year follow up[37]. This paper does not clearly define levels of depression or other risk factors and conflates stroke with TIA in its statistical analysis. It does find that depressive symptoms increase the risk of cerebro-vascular events in those aged over 65.

Ohira et al. followed “rural Japanese” participants aged 40-78 for 10 years[35]. Stroke is well defined and assessed in this study. Depression, although measured using an appropriate self-report instrument, is not defined to standard diagnostic criteria. This study did find depression to be a risk factor for stroke, but, as the authors note, the population used may limit generalisability to other cultures.

Surtees et al. followed UK participants who had initially engaged in large scale cancer study for 8.5 years[23]. Their participants ranged from 41-80 years old at entry. Depression was well defined, but the measures used to assess Major Depressive Disorder and “Psychological Distress” were applied with quite different time-frames for participants to recall (1 year vs. 4 weeks). The authors acknowledge that this may lead to over-endorsement of “Psychological Distress” due to recency. “Psychological Distress” but not Major Depressive Disorder was found to be a risk factor for stroke. However, this finding was not statistically significant.

Nilsson et al. drew on a national (Danish) register of hospital patients[34]. The age range is not specified, but mean age at entry varies across diagnostic groups from 50.6 (SD 18) to 66.6 (SD 13.4). The use of a national database conferred some advantages. The study had a very large sample (n=95,128) and the ability to compare outcomes across two “unwell” groups; those hospitalised with

depressive illnesses and those hospitalised with osteo-arthritis, both groups being followed up after discharge. Unfortunately this also limited the study in some key ways. Follow-up ranged from 1 day to 17 years. The basis of the depressive diagnoses was less clear than those for stroke. Also, the authors did not have access to data about other key risk factors. The study did find depression to be a risk factor for stroke, when compared with incidence for the osteo-arthritis group.

To summarise findings for this group of seven papers, although all found depression to be risk factor for stroke the quality of the papers tended to be lower than the previously discussed "age typical for first onset stroke" group. This is reflected in slightly lower overall PICO scores (mean of 19.2 compared to a mean of 21.7 for the previous group). The difference is most evident in the number of studies scoring less than half in the "Intervention" category (5 of 7, compared to 3 of 8 in the previous group). Larson et al. present the clearest evidence of depression being a risk factor for stroke, scoring adequately across all PICO categories[29]. They account well for other risk factors and derive an adjusted Hazard Ratio of 1.73 across genders. Jonas et al. also presents reasonably clear evidence, although they do not account for other risk factors as well, and the Hazard Ratio of 2.67 they derive is unadjusted[30]. The other studies in this group derive Hazard Ratios ranging from 1.08 to 3.43 (for participants under 65) [37] [23].

There were also two studies [32] [31] which focussed on particular age ranges that may be regarded as outliers. Liebetrau et al. are unique in focussing on first incident stroke in those over 85 years old at entry to study[32]. Their follow up period is shorter than most of the other studies at 3 years, and their sample is also relatively small (n=494). This includes 147 participants with a diagnosed dementing illness. This study scored adequately across PICO categories and found depression to be a risk factor

for incident stroke with an associated Hazard Ratio of 2.6. However, this finding was not statistically significant.

By contrast, Lee et al. have a distinctively young sample (18-44) and also one of the more overtly depressed, all depressed participants having been hospitalised for depressive disorders [31]. They, and a non-depressed comparison group, were followed up for 5 years. After adjustment for socio-demographic variables, co-morbid medical disorders and substance abuse the depressed group had a Hazard Ratio of 5.43 for incident stroke. This is in contrast with the non-depressed group's Hazard Ratio of 1.0 and the more modest Hazard Ratios found in other age cohorts. The study performs adequately across PICO criteria but acknowledges that it lacks data on health behaviours.

Single gender studies

Three of the studies focussed on a single gender, two looking at men [33] [28] and one looking at women[39]. They are considered separately here on that basis.

May et al. explored a cohort of men aged 45-59 who were already enrolled in epidemiological research into cardio-vascular illness[33]. However, their study does not account for several established risk factors including blood cholesterol, arterial disease, atrial fibrillation or previous stroke history. It performs adequately across other PICO categories. May et al. do find depression to be a risk factor for stroke, with an unadjusted Hazard Ratio of 1.26. However, statistical non-significance can be inferred from the surrounding Confidence Intervals.

Gump et al. explored a cohort of men aged 35-57 at entry to a large epidemiological study[28]. Although Gump et al. did not appear to define depression to standard diagnostic criteria the study performed adequately across other PICO categories, accounting particularly well for other risk

factors. Follow up was also relatively long, at 18 years. The authors found depression to be a risk factor for stroke with a Hazard Ratio of 2.03 for the quintile endorsing the highest number of depressive symptoms.

Strodl et al. explored a cohort of women aged 70-75 at entry to existing epidemiological research[39]. The study has good descriptive data on the population studied and adequate information on other risk factors. However, depression is not defined to standard diagnostic criteria or assessed using an appropriate depression-focussed measure. Stroke is also assessed based on participant self-report of diagnosis. This is reflected in a low overall PICO score of 17/32. Depression is found to be risk factor for stroke in this population.

Table 1, below, shows the outcome of the review process. The overall score for each study is given in the first column, below the lead author's name and the year the study was published. The PICO category scores are given in the last 4 columns.

It was decided to include some extra information in the intervening columns to add context and give easy oversight of the findings. This includes a brief description of each study's conclusions, number of participants, country of origin and the most generalisable statistical findings.

Table 1 – Papers reviewed, basic information and PICO scores

Lead Author **Year** **Score**	**Type**	**Brief Summary of Outcome**	**Statistic Used**	**Female**	**Male**	**Both**	**95% CI for Both**	**Sig for both?**	**Mechanisms?**	**N in study**	**Country**	**P/ 7**	**I/ 5**	**C/ 15**	**O/ 5**
Arbelaez[13] **2007** **21/32**	Prospective	Depression increased risk of stroke	Cox HR	N/R	N/R	1.26 adj, isch only	1.03 – 1.54	N/R but <0.05*	Inflammation considered, but unsupported	5,225	America	4	2	10	5
Bos[24] **2008** **24/32**	Prospective	Depressive symptoms (but not DSM-IV depression) a strong risk factor for men but not women	Cox HR	0.62 adj	1.63 adj	1.21 adj	0.80 – 1.83	N/R but >0.05*	Discussed, primarily as a version of the vascular depression hypothesis	4,224	Holland	7	3	9	5
Colantonio[26] **1992** **23/32**	Prospective	Depression increased stroke risk but effect made non-significant when other factors combined	Cox HR	N/R	N/R	1.23	1.05 – 1.44	<0.05	Discussed but no conclusion	2,812	America	5	3	10	5
Everson[27] **1998** **20/32**	Prospective	Depression increased risk of stroke mortality	Cox HR	N/R	N/R	1.54 adj	1.06 – 2.22	0.02	Discussed but no conclusion	6,676	America	6	1	9	4
Gump[28] **2005** **26/32**	Prospective but at risk population identified at start	Depression increased risk of stroke	Cox HR	N/R	N/R	2.03 adj for most depress quintile	1.20 – 3.44	<0.01	Very briefly discussed, broadly supportive of model similar to vasc dep hypothesis	12,866	America	5	2	14	5
Jonas[29]	Prospective	Depression	Cox HR	1.68	1.52	1.73	1.30 –	N/R	Discussed,	6,095	America	6	5	9	4

Table 1 – Papers reviewed, basic information and PICO scores

2000 **24/32**		increased risk of stroke		adj	adj	adj	2.31	but <0.05*	vascular depression as precursor not supported						
Larson[30] **2001** **21/32**	Prospective	Depression increased risk of stroke	Rel. Risk	1.46	N/R	2.67	1.08 – 6.63	N/R but <0.05*	Discussed but no conclusion	1,703	America	7	4	7	3
Lee[31] **2008** **20/32**	Prospective	Severe depression increased risk of stroke in young people	Cox HR	N/R	N/R	5.43 adj, patients aged 18-44	3.47 – 8.51	<0.01	Discussed but no conclusion	827	Taiwan	5	4	8	3
Liebetrau[32] **2008** **26/32**	Prospective	Depression increased risk of 1st incident stroke	Cox HR	2.9	1.4	2.6	1.5 – 4.6	<0.10	Discussed but no conclusion	494	Sweden	7	3	11	5

Table 1 – Papers reviewed, basic information and PICO scores

May[33] **2002** **18/32**	Prospective	"Psychological distress" is a predictor of fatal ischemic stroke but not of non-fatal ischemic stroke or TIA	Cox HR	N/R	N/R	1.26	0.85 – 1.85	N/R but >0.05*	Discussed but no conclusion	2,201	UK	4	3	7	4
Nilsson[34] **2004** **12/32**	Compares subsequent CVD in patients with depressive disorders vs. osteoarthritis	Severe depression with admission to hospital correlated with increased CVD	Cox HR	N/R	N/R	1.22	1.06 – 1.42	N/R but <0.05*	Not discussed at length	95,128	Denmark	4	2	2	4
Ohira[35] **2001** **22/32**	Prospective	Depression increased risk of stroke among Japanese	Cox HR	N/R	N/R	1.9 adj	1.1 – 3.5	N/R but <0.05*	Discussed but no conclusion	901	Japan	5	2	10	5
Ostir[36] **2001** **21/32**	Prospective	Increase in depression score increased risk of stroke	Cox HR	1.03	1.09	1.04	1.01 – 1.09	0.03	Discussed but no conclusion	2,478	America	4	4	9	4
Salaycik[37] **2007** **16/32**	Prospective	Depression increased risk of stroke for those under 65	Cox HR	N/R	N/R	0.78 adj, age 65+	0.46 – 1.34	0.374	Discussed but no conclusion	4,120	America	5	2	7	2
						3.43 adj, age <65	1.60 – 7.36	0.002							

Table 1 – Papers reviewed, basic information and PICO scores

Simons[38] **1998** **20/32**	Prospective	Depression increased risk of stroke , among other risk factors	Cox HR	N/R	N/R	1.41	1.01 – 1.96	<0.05	Discussed but no conclusion	2,805	Australia	5	2	9	4
Simonsick[12] **1995** **17/32**	Prospective	High depressive symptoms in Older Adults with diagnosed hypertension increases risk of stroke	Arithmetic comparison of stroke rates between those with "high" and "low" endorsement of depressive symptoms and pre-existing hypertension. "Rates of stroke were 2.3 to 2.7 times higher in most sub-groups with high depressive symptomatology"						Discussed, mainly focussed on hypertension	10,924	America	4	1	10	2
Strodl[39] **2008** **17/32**	Prospective	"Poor mental health" a risk factor for the self-report new diagnosis of stroke in older women	Odds Ratio	1.61	N/R	N/R	1.01 – 2.55 (for older women only)	<0.05	Discussed but no conclusion	7, 458	Australia	6	0	9	2
Surtees[23] **2008** **20/32**	Prospective	Psychological distress but not MDD predictive of stroke	Cox HR	1.03	1.12	1.08	0.67 – 1.75	N/R but >0.05*	Discussed but no conclusion	20,627	UK	4	2	10	4
Whooley[40] **2008** **23/32**	Prospective	Depression increased risk of subsequent vascular events [incl. stroke] but this effect was attenuated by health behaviours	Cox HR	N/R	N/R	1.05	0.79 – 1.40	0.75	Discussed but no conclusion	1,017	America	6	4	10	3

Table 1 – Papers reviewed, basic information and PICO scores

Wouts[41] **2008** **25/32**	Prospective	Depression increased risk of stroke	Cox HR	N/R	N/R	2.18 in combination with cardiac disease	1.17 – 4.09	0.02	Discussed, particularly role of cardiac problems	2,965	Holland	7	4	10	4

Cox HR = Cox Hazard Ratio

adj = adjusted for the other risk factors considered in that study

isch only = only refers to risk of ischaemic stroke

N/R = not reported

*=inferred from 95% Confidence Intervals

Discussion

This systematic review has as a central question "Is depression a risk factor for stroke?" In answering this we must consider in some depth what the reviewed papers can tell us. First of all, it is important to consider what question each paper is seeking to answer. Although all broadly tackle the question, they vary in specifics. For example, some discuss only women [39] and some consider only younger patients [31]. In addition, some are constrained in their approach to the index conditions, for example focussing on ischaemic stroke [13] or depression leading to hospitalisation [34].

The strongest evidence is from thestudies grouped by "Age at entry to study typical for first onset stroke". This group captures the population most likely to have a first stroke. It also benefits from generally adequate study quality and consensus across seven of the eight studies that depression is a risk factor for stroke, although with a relatively modest effect size (HR's 1.04 to 1.41.

The papers grouped by "Age at entry to study includes participants atypical of first onset stroke" are of more variable quality. For those studies not focussed on specific age ranges, it is less reliable to extrapolate findings from data concerning a range of underlying baseline incidences of stroke. The PICO scores reflect generally poorer methodology in this group. Depression is not well operationalised in several of these papers. The papers do show broad consensus in finding depression to be a risk factor for stroke, but the range of effect size is wider (HR's 1.08 to 3.43) [37] [23]. The papers addressing more specialised populations also find depression to be a risk factor for stroke. By the nature of these studies, and the relative lack of replication, it is perhaps more difficult to generalise from their findings.

Overall, the most balanced range of category scores are found in papers by Bos [24], Jonas [29], Ostir [36], Wouts [41] and Colantonio [26]. The first four of these papers report stroke as a risk factor for depression

across their whole sample, with a Hazard Ratio ranging from 1.04 to 1.73. However, Wouts et al. findings relate to the stroke risk found when depression and existing cardiac problems are combined[41]. The statistical findings reported by Colantonio et al. and Ostir et al. are not adjusted to account for the other risk factors they assessed[26,36] and Colantonio et al. note that the effect is not evident when other risk factors are accounted for.

Bos et al. and Jonas et al. do adjust for other risk factors, and indicate Hazard Ratios of 1.21 and 1.73 respectively[24,29]. The findings of Bos et al [24] do not attain statistical significance at the 0.05 level, based on the reported Confidence Intervals. However, on the same basis the findings of Jonas et al [29] do attain statistical significance at the 0.05 level. Therefore, a balanced consideration of the evidence still supports the contention that depression is a risk factor for stroke, but the extent of this effect is less certain. The effect does survive adjustment for other risk factors in 5 other studies that scored at least 20/32 overall. This is suggestive of at least one as yet unspecified mechanism that links depressive symptoms to subsequent stroke.

Many of the papers discuss potential mechanisms but do not reach strong conclusions. There appear to be several main candidates at present, although none is strongly supported by evidence. Mechanisms currently under debate include inflammation [13], platelet function [30] and hypertension [12]. Neu [42] carried out a pilot study using neuro-imaging to explore cerebro-vascular reactivity in people suffering major depressive disorder. Cerebro-vascular reactivity is an index of the dilation of blood vessels in relation to stimuli, which in turn would impact on blood pressure. Although based on a small sample, it indicated that those suffering depression and those who smoked had lower cerebro-vascular reactivity than non-depressed or non-smoking controls.

Another possible mechanism is via the impact of depression on heart disease, which is an established risk factor for stroke [43]. This causal chain would depend, however, on depression being a clear risk factor for heart disease. Nicholson [44] provides a meta-analysis of 54 studies which concludes that "Depression has yet to be established as an independent risk factor for CHD because of incomplete and biased availability of adjustment for conventional risk factors and severity of coronary disease". That is, depression may require a further mediator to impact on risk for coronary heart disease. Health behaviours have again been suggested as a likely mediator [45]. However, this makes the case for a depression – heart disease – stroke model less compelling by introducing a further element which is not yet well understood.

Whooley [46] in a separate paper [11] strongly endorses poor health behaviours secondary to depression as explaining the link between depression and a range of vascular events. This has good face validity as a co-dependent risk factor. However, it is not entirely convincing as an independent risk factor. As noted, several studies indicate that the effect survives adjustment for risk factors such as smoking, body mass and high blood cholesterol. Such factors could be considered indexes of health behaviour. This suggests that the mechanism whereby depression impacts on stroke incidence is to some extent independent. Whooley specifies physical activity as a significant health behaviour, with low physical activity increasing stroke risk [11]. Only 3 of the other reviewed papers assess and report physical activity [12,29,39]. Of these, only Strodl et al. reports the impact of physical activity on risk of stroke, finding higher levels physical activity to be a protective factor[39].

The role of age as a mediator is not clear, but may bear further examination. Lee [31] found that "severe depression" leading to hospitalisation in people aged 18 to 44 evinced a strikingly large Hazard Ratio of 5.43. This was after adjustment for other risk factors, although Lee et al. did not include key risks such as smoking and obesity. Also, Lee et al. use severe depression (requiring

hospitalisation) as an index, which limits the generalisability of their findings[31]. It should also be borne in mind that the underlying rate of stroke for this age group is much lower than that of the 45+ age group. Although this study was unique in its focus on people aged 18 to 44, some of the other studies did include younger participants [29 30 37 27 34]. Jonas et al. recruited participants from 25 – 74 years old, but do not report the impact of age on depression as a risk factor for stroke [29]. They also note that 5-year increases in age independently increase the relative risk of stroke at a ratio of 1.59. Larson et al. recruited participants aged from 18 to 65+ (no upper limit is reported). They also report age effects independent of depression. Again, a consistent increase in stroke risk with rising age is noted[30]. Salaycik et al. differentiate between participants older and younger than 65 years, finding that depression was only a risk factor for those over 65. Salaycik et al. recruited participants aged 29-100 years. They note an increase in relative risk for stroke with each 10-year age increase[37]. Everson et al. and Nilsson et al. do not provide age stratified information[27,34]. The aetiology of stroke for young adults is different, with ischaemic stroke more linked to embolism and cervical artery dissection than atherosclerosis and a higher incidence of haemorraghic strokes than in older adults [47,48]

Conclusions

Overall, despite the variable study quality, the consensus across 19 of 20 studies that depression is in some way a risk factor for stroke is suggestive of a robust finding. This is clearest for the group of studies which use samples typical of the population most likely to have a first stroke.

It is less clear whether depression only enhances the effects of other risk factors or whether it has some independent effect. Depression is likely to impact on a range of health behaviours [49] as well having its own biological sequelae, so it is improbable that it would only act as an independent risk factor.

There is evidence suggestive of some independent role as many known risk factors are adjusted for across the studies, but an excess effect of depression remains. The variability of study quality makes the independent effect size for depression unclear, but it appears to be of the same order as that for several established risk factors such as smoking. However, it is possible that this could be a statistical artefact. For example, it could reflect an amplification and interaction of other risk factors beyond their individually measured effect.

For depression to act as an independent risk factor there would have to be at least one mediating biological mechanism. The mechanism(s) involved have not been clearly established in any of the reviewed papers, but candidate mechanisms such as inflammation, platelet function and cerebro-vascular reactivity may warrant further investigation. As this is likely to be technically demanding and have high associated resource costs it may be useful to concentrate such investigation on that section of the population most at risk of first stroke. The age at which stroke incidence rises sharply varies from country to country, but is typically in the 40-50 year old range.

Most of the studies reviewed here are at an epidemiological level, presumably requiring extensive resources. There is not a clear case for establishing new studies of this type solely to explore further whether depression is a risk factor for stroke. However, where epidemiological studies are already under way careful selection of diagnostic criteria and tools for the index conditions, particularly depression, would enhance the utility of the findings. Stratification of findings by age range may also be useful because of different stroke aetiologies in younger adults. In clinical terms, the indication that depression is a risk factor for stroke has several implications. At a preventative and public health level it may be useful to raise awareness of depression as a risk factor for stroke. This could

be linked both to assessment and intervention. For example, diagnosis of depression could prompt investigation of other risk factors and vice-versa.

Research indicating exercise is an effective intervention for depression originated with the treatment of mild to moderate depression in younger adults, but is now beginning to be supported for older adults and for Major Depressive Disorder [50,51]. This is significant as there is a suggestion that lack of physical activity could itself be a risk factor. Regular exercise could reduce depressive symptoms and also other stroke risk factors such as obesity and hypertension. The beneficial effects of this would therefore transcend aetiology. For example, even if the vascular depression hypothesis was supported by further research, suggesting direct treatment of depression would be ineffectual, exercise would remain beneficial.

That depression impacts on risk of stroke now seems established. However, this review comprises what may be considered an emerging and therefore changeable literature. It has not provided detailed technical analysis or synthesis of the potential mechanisms. Similarly, detailed consideration of the known medical risk factors that inform many of the studies is beyond the scope of the present review. More expert consideration of these could be useful in prioritising future research. There is also scope for a statistical meta-analysis of the reviewed papers. This might clarify the effect size of depression as a risk factor for stroke and the extent to which this is independent of other risk factors. The ongoing questions are; to what extent depression acts as a risk factor for stroke, via what mechanism, and with what treatment implications?

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Chapter 2

Major Research Project

Prepared in Accordance with Requirements for Submission to

Stroke

Self Report Questionnaire Assessment of Anxiety and Depression amongst Stroke Patients in Rehabilitation Settings

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Abstract

Background and purpose: Depression and anxiety are common stroke sequelae and are detrimental to outcomes if not detected and addressed. Some self-report measures of anxiety and depression have been criticised for lack of specificity and face validity of item structure [Hospital Anxiety and Depression Scale - HADS] or may not be fully validated for a stroke population [Geriatric Depression Scale Short Form - GDS-SF]. A recently developed anxiety measure may be useful for this population [Geriatric Anxiety Inventory - GAI]. The purpose of the study is to assess the clinical utility of these measures for screening mood disorders in people over 45 years old undergoing stroke rehabilitation.

Methods: The HADS, GAI and GDS-SF were assessed against DSM-IV "gold standard" diagnoses from the Mini International Neuropsychiatric Interview [MINI]. A sample of patients in rehabilitation following stroke (n=34) was used. The age range was 46-92 (mean 73.12 years; SD=12.37). 21 participants were female and 13 were male (61.8% and 38.2% respectively). The study sample had relatively intact cognitive function as assessed by referring clinicians and relatively high communicative ability with Frenchay Aphasia Screening Test [FAST] scores in the range 18 to 30 (mean 26.38; SD=2.94).

Results: All measures were able to distinguish those with index disorders from those without. HADS-A displayed sensitivity 91%, specificity 70% at a cut-off of 8/21. HADS-D displayed sensitivity 82%, specificity 83% at a cut-off of 8/21. GAI displayed sensitivity 91%, specificity 65% at a cut-off of 8/20. GDS-SF displayed sensitivity 63%, specificity 87% at a cut-off of 8/15.

Conclusions: All conclusions are tentative as this is a small scale preliminary study. The HADS performed best in screening for anxiety and depression, and is suitable for use with a cognitively intact stroke population. The GAI also performed well and is suitable for use with this population. The GDS-SF had poor sensitivity and so does not appear suitable for this population.

Introduction

Stroke is an umbrella term for loss of oxygenated blood supply to one or more brain areas, typically causing impairment to the functions supported by the affected areas. To be classified as a stroke and not a Transient Ischaemic Attack [TIA] this impairment must last over 24 hours [40]. The impairment can be cognitive, emotional or physical in nature.

The World Health Organisation [WHO] estimates that each year 15 million people world-wide suffer stroke, including TIA. Of these, 5 million die and 5 million develop permanent disability[1].

The Information Services Division in Scotland [ISD Scotland] reports rates of incidence for Cerebrovascular Disease [CVD] in Scotland. Provisional data for 2009 shows the incidence for both sexes rises sharply after age 45. Incidence in the 0-44 age range was 572. In the same period the incidence for people in the 45-64 age range was 2692. For the 65-74 age range the incidence was 7121.[2]

Depression and anxiety have been identified as common sequelae of stroke [3]. Hackett, Anderson, House, & Halteh (2008) [4] note that although depression may influence recovery and outcome following stroke, many, perhaps most, patients do not receive effective treatment because their mood disorder is undiagnosed. There is therefore widespread agreement that early recognition and active management of post-stroke mood disorder is desirable. Research on post-stroke mood disorder has largely focussed on depression, perhaps reflecting a well studied correlation between depression and poorer outcomes including increased mortality [5]. It may also reflect the hierarchical approach to psychiatric classification, in which anxiety diagnoses are subsumed by depression diagnoses [6]. However, Thompson (2000) notes that anxiety also can impede engagement and motivation in the context of stroke rehabilitation [7]. This is supported by findings from studies

exploring prevalence [6] [8] which suggest that Generalised Anxiety Disorder [GAD] and Agoraphobia may be the most common anxiety disorders following stroke.

The recently published Scottish Intercollegiate Guidelines Network [SIGN] Guideline 118 (2010) "Management of Patients With Stroke" notes that stroke patients are at risk of treatable mood disorders and that "all stroke patients (including those cared for in primary care) should be screened for mood disturbance". Assessment prior to discharge plus follow up assessment is indicated [9].

Self-report questionnaire measures can provide a quick way to carry out initial screening for mood disorders and therefore direct appropriate treatment if required. Some reviews of such measures have found them acceptable [10]. Others have found their usefulness to be constrained by poor specificity [11]. However, it may be argued that for purposes of initial screening in a clinical environment, sensitivity is more important than specificity.

The present study explores the clinical utility of three different measures of mood disturbance in patients aged 45 or over following a stroke. More specifically, the study considered the Hospital Anxiety and Depression Scale[HADS] [12] for screening both anxiety and depression, the Geriatric Anxiety Inventory [GAI] [13] for screening anxiety and the Geriatric Depression Scale – Short Form [GDS-SF] [14] for screening depression.

Two studies [15] [16] have suggested that the HADS is a valid measure of mood disorder, including anxiety, in people who have had a stroke. However, there are several indicators that the HADS, although acceptable, might not be optimal for use with a stroke population. The HADS, despite being created for an unwell population, contains some somatic items (e.g. "I feel as if I am slowed down") that may be over endorsed amongst a stroke population. It also has a 4-choice response format that is more complex than measures with a 2-choice response format. A literature review of

HADS-based studies [17] noted that it performed well as a bi-dimensional test (anxiety and depression). However, there was overlap between items, and optimal cut-offs varied across populations. This in itself may not be problematic: Carr (2006) notes "anxiety and apprehension" as clinical features of depression [18]. However, a factor analysis of the HADS in relation to patients with Acquired Brain Injury [ABI], including stroke, found a three factor structure with the third factor not mapping well onto anxiety or depression [19]. That is, HADS appears to be sensitive to a factor in ABI patients which is neither anxiety nor depression, but rather an artefact of the scale.

Although not specific to stroke, a study by Dunbar et al. (2000) found that the "Tripartite Model" of mood disturbance mapped well on to the factors tapped into by the HADS [20] [21]. The Tripartite Model proposes that anxiety and depression share an underlying "negative affectivity" but can be most clearly distinguished by levels of "physiological hyperarousal" and "anhedonia" respectively. Dunbar et al. found that the depression sub-scale of the HADS mapped well onto anhedonia, but the anxiety sub-scale was mixed between items reflecting physiological hyperarousal and more generalised negative affectivity.

The GAI was specifically developed as a measure of anxious cognitions in geriatric populations. The authors demonstrated its effectiveness in detecting GAD in this population (Sensitivity 75%, Specificity 84%). The GAI was designed to be suitable for the over-60 population. Design features include brevity (20 items), dichotomous response format and less reliance on potentially misleading somatic symptoms. These features may also be helpful in assessing adult patients who have had a stroke. It is as yet untested with a stroke population. Indeed, there seem to be few measures of anxiety that have been validated for post-stroke populations. This could be both a cause and effect of the relative rarity of research in this area.

The GDS-SF is a 15 item questionnaire with a dichotomous response format. It is drawn from a longer 30 item version – the Geriatric Depression Scale [GDS]. At the time of writing there were no validation studies for the 15 item version in stroke populations.

However, there is some support for the use of the 30 item GDS with stroke populations. Agrell et al. (1989) found the GDS to perform acceptably for a stroke population in a range of settings (rehabilitation, day outpatient and nursing home) with a cut-off of 10/11 (Sensitivity 88%, Specificity 64%, PPV 58%, NPV 88%) [22]. Johnson et al. (1995) found that a GDS cut-off of 10/11 yielded acceptable performance for detecting depression in a community based sample (Sensitivity 84%, Specificity 66%, PPV 53%, NPV 90%) [23]. Interestingly, they also assessed the performance of the GDS in detecting anxiety although it was not designed for this purpose. They found that with a cut-off of 14/15 it was also somewhat able to detect anxiety disorders (Sensitivity 65%, Specificity 79%, PPV 51%, NPV 86%).

Thus, there is a modest evidence base for the use of the 30 item GDS with stroke patients undergoing rehabilitation. The evidence supporting use of the 15 item version with patients who have some degree of cognitive impairment is more mixed and does not directly address a stroke population. Friedman et al. (2005) found it to perform acceptably in detecting depression among a functionally impaired but cognitively intact older population [24]. Burke et al. (1991) found it to compare acceptably with the 30 item version in a cognitively intact population, but performed less well amongst patients with mild Alzheimer type dementia [25]. Lesher et al. (1994) found both versions to perform acceptably in patients with a range of presentations including depression, thought disorder and dementia [26]. Anecdotal report suggests that the GDS-SF is frequently used with stroke patients despite not being clearly validated for this purpose. This highlights the importance of investigating the validity of this measure for stroke patients.

The GDS-SF and GAI share several design features that suggest they could be particularly useful for an older stroke population. If they are found to perform equivalently to the HADS such design features may suggest they would be a better choice of measure in patients with stroke. Both the GAI and GDS-SF are specifically designed for use with an older population, which reflects the demographics of stroke well. In terms of specificity, questionnaires designed around a single presenting complaint may be expected to perform better. Although less brief than the HADS, the GAI and GDS-SF are both purposely brief, thus limiting participant fatigue. A particular strength may the dichotomous response format of both GAI and GDS-SF, which is likely to be less vulnerable to visuo-spatial disruption or cognitive difficulties than the 4-item response format of the HADS. The instructions to patients given with both the GAI and GDS-SF are briefer than those given with the HADS. The GAI and GDS-SF also have less focus on potentially over-endorsed somatic symptoms than the HADS.

The present study provides more information on the suitability of the GAI, GDS-SF and HADS for a stroke population. The findings of these measures are compared to a "gold standard" structured clinical diagnostic interview, the Mini International Neuropsychiatric Interview [MINI] [27].

If the GAI and GDS-SF are found to be suitable for detecting mood disorders in a stroke rehabilitation population it will provide stroke clinicians with an alternative to the HADS that may be preferable for some of the pragmatic reasons outlined previously, being potentially easier to complete and less vulnerable to over-endorsement of somatic items. A brief evaluation of each measure's acceptability to stroke patients is also included.

As previously argued, sensitivity may be more important than specificity for clinical screening measures as further investigation can tease out relevant diagnoses. Given this, and the findings of

the previously discussed research on the HADS, GAI and GDS, the present study will regard sensitivity ≥ 75% and specificity ≥ 65% as benchmarks for clinical utility.

Primary Research Questions:

The primary research questions fall into two main classes. Firstly, will the self-report measures successfully distinguish those who meet DSM-IV criteria for index disorders from those who do not? Secondly, do the self-report measures have sufficient sensitivity and specificity to make them useful clinical screening tools for their respective index disorders following stroke?

Hypotheses

Participants meeting a DSM-IV anxiety disorder criteria will have higher scores on the GAI than those who do not, at a statistically significant level ($p \leq 0.05$)

Participants meeting a DSM-IV depressive disorder criteria will have higher scores on the GDS-SF than those who do not, at a statistically significant level ($p \leq 0.05$)

Participants meeting a DSM-IV depressive disorder criteria will have higher scores on the HADS-D than those who do not, at a statistically significant level ($p \leq 0.05$)

Participants meeting a DSM-IV depressive disorder criteria will have higher scores on the HADS-D than those who do not, at a statistically significant level ($p \leq 0.05$)

The GAI will detect anxiety disorders with a sensitivity of ≥ 75% and a specificity of ≥ 65%

The GDS-SF will detect depression with a sensitivity of ≥ 75% and a specificity of ≥ 65%

The HADS anxiety sub-scale will offer equivalent sensitivity but inferior specificity to the GAI

The HADS depression sub-scale will offer equivalent sensitivity but inferior specificity to the GDS-SF

Methods

Participants and Recruitment Procedures

Potential participants were sought via ward staff or clinicians working in outpatient clinics. Referrers were provided with information regarding the study, its inclusion and exclusion criteria, and considered each potential patient's capacity to consent to participate in research. Potential participants considered to have capacity to consent were provided with an information sheet regarding the study, inviting them to consider participation. The sheet also discussed consent and the right to withdraw at any time.

After a minimum 24-hour period for consideration, patients who expressed an interest in participation were given the opportunity to ask the researcher further questions about participation. Written consent was solicited before procedures begin.

Inclusion and Exclusion Criteria

Inclusion criteria:

The study sought adults aged 45 or over who were undergoing rehabilitation following a stroke and were therefore in-patients on a ward or attending out-patient at a clinic that referred to the study.

Exclusion criteria:

The study excluded those suffering motor or cognitive conditions severely affecting communication (e.g. dysarthria, apraxia of speech, aphasia), or who lacked capacity to safely consent and take part. Those suffering from current psychosis or with recent history of serious substance misuse were also excluded.

Design

Research Procedures and Equipment

Information on participants who consented to participate was accessed from medical records resting with the relevant ward or clinic. This included age, sex, deprivation category [DEPCAT] derived from post code and, where available, stroke localisation.

Participant cognitive function was not formally assessed as part of this research protocol. However, as noted in the Exclusion criteria, referral in to the study by stroke clinicians included their clinical judgment of the patient as having sufficient cognitive state and capacity to safely take part. This was not felt to be onerous on patients or clinicians as it forms part of routine clinical practice. In some cases this clinical judgement would have involved use of standard measures, such as the Mini Mental State Exam, but not necessarily in all. Asking participants to complete cognitive testing in addition to an existing 90-minute research protocol was therefore felt to be an unnecessary and potentially fatiguing demand on people still recovering from stroke.

Participants were informed that reading was required in order to complete some measures and that a brief assessment of language ability would be administered first.

Following Salter's (2006) [28] review of post-stroke aphasia screening tools for use by those without expertise in Speech and Language Therapy, the Frenchay Aphasia Screening Test [FAST] [29] was used to assess linguistic ability. Salter [28] reports that this measure has robust validation, tests comprehension of written material and also benefits from brevity (5-10 minute completion). The FAST was used to ensure that patients had sufficient reading ability to complete subsequent tasks and to quickly pick up on communication difficulties at the start of the procedure. Where participants were unable to write due to physical disability (n=9), the FAST was pro-rated.

Participation following FAST administration was structured as follows. The Mini International Neuropsychiatric Interview [MINI] was administered first, to provide psychiatric diagnoses according to DSM-IV. The MINI is a semi-structured interview in which the assessor asks the patient directly about diagnostic criteria and follows a heuristic to generate diagnoses. It has been designed for quick administration, estimated at 15 minutes in a non-stroke population, reducing the risk of participant fatigue. The MINI's authors found that its diagnostic utility compared favourably with other, more time consuming measures such as the Structured Clinical Interview for DSM-III, Patient Version [SCID-P] and Composite International Diagnostic Interview [CIDI] [30]. Validation studies for the MINI are primarily by its authors, apart from some studies validating non-English language versions. It was, however, the measure used in the development and validation of the GAI, and has been used in a validation study of the GDS-SF with cognitively intact but functionally impaired older people (Friedman et al., 2005) [24]. Pinninti et al. (2003) assessed the MINI as having good clinical utility and patient acceptability [31].

When compared with SCID-P diagnoses, Sheehan et al. (1997) found the MINI had good properties for detection of major depressive disorder (Sensitivity 0.96, Specificity 0.88, PPV 0.87, NPV 0.97) and for detection of current agoraphobia (Sensitivity 0.85, Specificity 0.88, PPV 0.69, NPV 0.95). Regarding reliability, the same study reports good reliability (kappa values) across 23 domains (inter-rater reliability ≥ 0.79 in all domains, test-retest reliability ≥ 0.75 in 14 domains). [30]

Following the MINI interview, participants were offered a minimum 30-minute break to prevent fatigue. They were then asked to complete the GAI, GDS-SF and HADS independently of the researcher. The measures were not titled (e.g. "Geriatric Anxiety Inventory") in order to avoid priming. The self-report measures were in large print to facilitate their completion.

Qualitative measures of acceptability, such as semi-structured interview are most likely to be useful if conducted immediately following completion of each scale in order to maximise participant recall. In this case, however, their use seemed inappropriate as they are likely to be onerous to patients. Consistent with the previously stated rationale for use of a dichotomous response format, the two extra items below were appended to each scale as a measure of acceptability.

1) Has this form been easy to complete? (Yes /No)
2) Has this form let you express your current state of mind? (Yes /No)

Measures

The principal measures in the study are HADS scores, GAI score, GDS-SF score, ease-of-use endorsements and self-expression endorsements.

Other Data

Other data amenable to statistical analysis were age, sex and deprivation category [DEPCAT] derived from post code.

Information available from patient notes on stroke localisation varied in detail and diagnostic method. This was not robust enough to support further analysis.

Ethics

This study was reviewed and approved by the NHS West of Scotland Research Ethics Committee and Research and Design Department. Participants were assessed for capacity to consent to participation in research prior to their consent being sought. The right to withdraw was emphasised. Participants could be prone to fatigue and distress so pacing of tasks and regular checking of fatigue levels was used.

The lack of intervention was made clear to participants. If any of the measures indicated untreated psychological difficulty this information was referred on to enable appropriate action to be taken.

Data Analysis Procedures

Data analyses were carried out using PASW Statistics 18, Release Version 18.0.0 [41]. Comparisons were planned and, where relevant, predicated upon single-tailed hypotheses. Assumptions for parametric analyses were tested.

Data was first analysed to yield descriptive statistics for the sample and its sub-groups.

The DSM-IV diagnoses yielded by the MINI can be viewed as demarcating different groups within the sample – those who have current anxiety or depression disorders and those who do not.

ANOVAs were used to explore differences in scores on the relevant measures (GAI,GDS-SF, HADS) between those who met DSM-IV criteria for anxiety or depression disorders and those who did not. Some participants met criteria for both anxiety and depression disorders. In such cases the analyses continued to be based on presence or absence of the currently considered index disorder (anxiety or depression). It was predicted that the disorder groups would have higher scores than the non-disorder groups.

Cronbach's Alpha was used to assess internal consistency of the GAI, GDS-SF, HADS-A and HADS-D.

Pearson's *r* was used to correlate participant scores on the GAI, GDS-SF, HADS-A and HADS-D.

Given concerns from the literature about the sensitivity and in particular specificity of measures, this information was also calculated and reported. Data on sensitivity and specificity was used to tentatively suggest optimal cut-offs for each measure with this population. As indicated above, sensitivity will be prioritised over specificity.

Justification of Sample Size

The sample (n=34) is smaller than that indicated by prognostic power calculations prior to the study. This indicated that ANOVA's were the measures most demanding of sample size, with each of the four groups within the sample requiring (n=21) or more.

The four groups in the study sample varied in size; those with no depressive disorder (n=23), those with no anxiety disorder (n=23), those with depressive disorder (n=11) and those with anxiety disorder (n=11).

However, the observed effect sizes were larger than that used in the pre-study calculations. When power calculations based on the actual sample and effect sizes for the ANOVA's were performed using G*Power 3.010 [32] [33] all were found to have power > 0.8.

Results

Participant characteristics

Participants came from 6 sources in Greater Glasgow: In-patient Ward 1 (n=17, 50%); In-Patient Ward 2 (n=3, 8.8%); In-Patient Ward 3 (n=6, 17.6%); Psychology Stroke Out-Patient Clinic (n=3, 8.8%); In-Patient Ward 4 (n=4, 11.8%) and Medical Stroke Out-Patient Clinic (n=1, 2.9%).

The participants in the study (n=34) were aged between 46 and 92 years old (mean 73.12 years; SD=12.37). In terms of gender, 21 were female and 13 were male (61.8% and 38.2% respectively).

FAST scores were in the range 18 to 30 (mean 26.38; SD=2.94).

DEPCAT indexes relative levels of deprivation based on postcode, ranging from 1 (most affluent) to 7 (most deprived). Study participants had the following DEPCAT's: 1 (n=4, 11.8%); 2 (n=5, 14.7%); 3 (n=2, 5.9%); 4 (n=4, 11.8%); 5 (n=2, 5.9%); 6 (n=12, 35.3%) and 7 (n=3, 8.8%). DEPCAT's were not obtained for 2 participants (5.9%).

For the purpose of analysis, the participants were split into four groups based on DSM-IV diagnoses generated by the MINI.

Settings

All recruitment took place across four stroke-equipped rehabilitation wards and two outpatient stroke clinics in Greater Glasgow. Recruitment occurred in a 5 month period from February to July 2010. Where possible, interviews and assessments were administered in a suitable room attached to or nearby the relevant ward or clinic. If in-patient participants had particular mobility issues or expressed a wish to be seen at bedside this was done.

Groups within the sample

For the purposes of analyses, participants could be placed within main four groupings. These are illustrated in Table 1, below.

Group	Total n	Female n (%)	Male n (%)	Mean age (SD, range)	Mean index condition score I (SD, range)	Mean index condition score II (SD, range)
Depressive disorder	11	8 (72.7)	3 (27.3)	69 (13.5, 46-82)	GDS-SF 8.6/15 (4.5, 1-13)	HADS-D 9.6/21 (3.7, 3-17).
Anxiety disorder	11	9 (81.8)	2 (18.2)	70 (15.6, 46-89)	GAI 12.5/20 (5.9, 0-20)	HADS-A 10.4/21 (4.6, 1-17)
No depressive disorder	23	13 (56.5)	10 (43.5)	75 (11.5, 55-92)	GDS-SF 4.0/15 (2.9, 0-11)	HADS-D 4.7/21 (3.4, 0-13)
No anxiety disorder	23	12 (52.2)	11 (47.8)	75 (10.5, 55-92)	GAI 4.9/20 (4.5, 1-13)	HADS-A 5.2/21 (3.7, 0-15)

Table 1 – Main groups within the study, and basic characteristics

There was some overlap between participant groups, with some participants having both anxiety and depression disorders, or having neither. This is illustrated in Table 2, below.

Group	Total n	Female n (%)	Male n (%)	Mean age (SD, range)	Mean depression measure scores (SD, range)	Mean anxiety measure scores (SD, range)
Both depressive and anxiety disorders	6	5 (83.3)	1 (16.7)	65 (15.8, 46-81)	GDS-SF 10.5/15 (3.1, 5-13)	GAI 14.0/20 (4.5, 8-20)
					HADS-D 11.5/21 (3.5, 8-17)	HADS-A 12.8/21 (2.9, 8-17)
No depressive or anxiety disorder	18	9 (50)	9 (50)	75 (11.1, 55-92)	GDS-SF 4.1/15 (3.0, 0-11)	GAI 3.6/20 (4.6, 0-14)
					HADS-D 4.6/21 (3.5, 0-13)	HADS-A 5.1/21 (3.8, 0-15)

Table 2 – Group overlap within the study, and basic characteristics

Analyses

Correlations

Pearson product-moment correlation coefficients were computed to assess the relationship between age, DEPCAT, gender, depression and anxiety in the study sample. There was no correlation between age and depression (r=-.234, n=34, p=.184), age and anxiety (r=-.187, n=34, p=.289); gender and depression (r=-.156, n=34, p=.378); gender and anxiety (r=-.285, n=34, p=.102); DEPCAT and depression (r=.228, n=34, p=.195) or DEPCAT and anxiety (r=.313, n=34, p=0.71).

As no correlation was found for age, gender or DEPCAT it was not necessary to co-vary for them in subsequent calculations.

Variance on questionnaire scores by condition

ANOVAs were used to assess the variance in scores between those with and without index conditions.

Results indicated that participants with anxiety disorder scored significantly higher on the GAI than those with no anxiety disorder ($F=15.36$, $df=1$, $p <0.001$). Participants with depressive disorder scored significantly higher on the GDS-SF than those with no depressive disorder ($F=12.96$, $df=1$, $p <0.001$). Participants with anxiety disorder scored significantly higher on the HADS-A than those with no anxiety disorder ($F=12.53$, $df=1$, $p <0.001$). Participants with depressive disorder scored significantly higher on the HADS-D than those with no depressive disorder ($F=14.63$, $df=1$, $p <0.001$).

Concurrent Validity

Pearson product-moment correlation coefficients were computed to assess the relationship between scores on GAI and scores on HADS-A. As expected, there was a significant association between these measures ($r=.687$, $n=34$, $p <0.05$). Similarly, for GDS-SF and HADS-D, a significant association between the measures was observed ($r=.705$, $n=34$, $p <0.05$).

Reliability

Cronbach's α was computed to assess the internal reliability of the questionnaires. All exceeded the benchmark value of 0.8 suggested by Field & Hole, (2003) [34].

The GAI (20 items) had a Cronbach's α of 0.934. The GDS-SF (15 items) had a Cronbach's α of 0.870. The HADS Anxiety scale (7 items) had a Cronbach's α of 0.836. The HADS Depression scale (7 items) had a Cronbach's α of 0.837.

Acceptability

Two additional questions were attached to each questionnaire: "Has this form been easy to complete? (Yes /No)" and "Has this form let you express your current state of mind? (Yes /No)".

91% of participants (n=31) said the GAI was easy to complete and 97% (n=33) said it let them express their current state of mind.

91% of participants (n=31) said the GDS-SF was easy to complete and 88% (n=30) said it let them express their current state of mind.

91% of participants (n=31) said the HADS was easy to complete and 97% (n=33) said it let them express their current state of mind.

Due to the unitary construction of the HADS it was not appropriate to generate separate acceptability ratings for HADS-A and HADS-D.

Clinical Cut-offs, Sensitivity and Specificity

Receiver Operating Characteristic [ROC] curves were used to assess the sensitivity and specificity of the measures, as well as indicating optimal cut-offs. This study selected sensitivity ≥75% and specificity ≥65% as indicating clinical utility, based on the values reported and cut-offs used in the original validation study for the GAI [13]. This reflects the relative priority given to identifying patients with index disorders when assessing a screening measure. In summary, all questionnaires met or exceeded these criteria for clinical utility, except the GDS-SF which fell short in terms of sensitivity. This is illustrated in Table 3, below.

Measure	Area Under Curve	95% CI	Cut-off	Sensitivity	Specificity
GAI	0.824	0.663-0.985	8/20	91%	65%
GDS-SF	0.791	0.607-0.974	8/15	63%	87%
HADS-A	0.820	0.652-0.988	8/21	91%	70%
HADS-D	0.846	0.705-0.987	8/21	82%	83%

Table 3 – Properties of the self-report measures

Discussion

All questionnaires were able to distinguish those with index disorders from those without, with a large effect size at a statistically significant level in all ANOVA's. [GAI (f=3.59); GDS-SF (f=2.15); HADS-A (f=2.43); HADS-D (f=2.31)]

The large effect sizes are indicative of clear differentiation between the groups. The high level of statistical significance implies that the effect is unlikely to be due to sampling error. This is important given the relatively small n involved in the study, and contributes greatly to the statistical power achieved by the analyses. Findings predicated on similar effect sizes and p-values with a larger n would be even more robust.

All the questionnaires were found to be acceptable to the large majority of participants, with minimal variation between them. All questionnaires showed acceptable internal reliability, with Cronbach's α ranging from 0.836 to 0.894. This indicates that items within questionnaires were largely measuring the same thing. It does not mean that they were necessarily measuring the index condition for which they were designed. This question is better addressed by considering variation in the sensitivity and specificity of questionnaires. This data is also of particular relevance to potential clinical use, and is discussed in more detail below.

GAI

As hypothesised, the GAI offers similar sensitivity to the HADS-A (both 91%). Contrary to hypothesis, the GAI offered inferior specificity to the HADS-A (65% and 70% respectively).

The original GAI validation study was conducted in a geriatric population [13], and showed sensitivity of 75% and specificity of 84% above a cut-off of 10. The present study found superior sensitivity (91%) but inferior specificity (65%) for a post-stroke population above a cut-off of 8. Area under ROC curve

in the original study (0.80) was similar to that found in the present study (0.82). Cronbach's α was also similar across the original and present study (0.91 and 0.93, respectively).

This suggests that the GAI is suitable for use in a post-stroke population, particularly where identification of anxious patients is a priority. A lower cut-off of 8 is indicated for this population. There are some factors which may incline clinicians to favour the GAI over the HADS. If a diagnosis of depression is already established, the GAI provides an anxiety focussed tool. For patients with limited cognitive or expressive capacity, the GAI's dichotomous response format may provide ease of administration. It lends itself to non-verbal responding, for example by pointing at YES / NO response cards. This should be weighed against the HADS superior specificity and long established use. The relatively poor specificity limits the GAI's usefulness as a research tool in a post-stroke population. However, it should be emphasised that this is a preliminary study to explore the utility of GAI in assessing anxiety in stroke survivors. Given this, and the study limitations discussed below, conclusions must be treated with some caution.

GDS-SF

Contrary to hypotheses, the GDS-SF offers inferior sensitivity to the HADS-D (63% and 82% respectively). The GDS-SF does have slightly superior specificity to the HADS-D (87% and 83% respectively). Previous research [22] [23] found the 30-item GDS achieved sensitivity of 84-88% and specificity 64-66% in a post-stroke population. In the present study, the 15-item GDS-SF had lower sensitivity of 63% but superior specificity of 87%.

This means the GDS-SF performed below the selected sensitivity benchmark for this study (75%). The benchmark is arbitrary, however the GDS-SF also performs poorly in comparison with the HADS and 30-item GDS. Therefore, on the basis of the present data, it cannot be recommended over more

robust alternatives for clinical or research use with a post-stroke population. This is potentially important, as anecdotal report suggests that the GDS-SF is used in some stroke services, despite a lack of previous validation studies. The present data suggest that this could lead to non-identification of patients with depression. Use of the GDS-SF may have been influenced by the good utility established for the thirty item GDS with this population. Again however, this is a preliminary research study, and the first to explore utility of the GDS-SF with stroke survivors. Replication and extension of this work will be important in developing a clearer picture.

HADS

The HADS-A performed better than predicted for a post-stroke population. Sensitivity of 91% and specificity of 70% were observed. This is superior to that of GAI, a measure designed solely to assess anxiety.

The HADS-D also performed better than predicted in the study. Sensitivity of 82% and specificity of 83% were well above those of a measure designed solely to assess depression (GDS-SF). The cut-off indicated by the present data (8) is at the lower end of those commonly used. Crawford et al. (2001) note that a score of 8-10 is generally regarded as indicative of "mild cases", but that a cut-off of 10-11 may be more clinically useful in the general population [35]. The lower cut-off suggested in the present study may be an artefact of the relatively small n in the present study. Further research will be required to tease out these issues.

Previous studies [15] [16] found the HADS to be suitable for use with a post-stroke population, but this contrasts with other work which raised doubts regarding the utility of the HADS in two respects. Dawkins et al. (2008) conducted a factorial analysis of the HADS in a cognitively impaired population, including stroke survivors [19]. This identified a factor linked to some items which was neither anxiety

or depression, but appeared to be an emergent property of some scale items. This implies that the HADS may lack specificity in detecting anxiety or depression with a cognitively impaired population. The present study data suggests that the HADS has good specificity for a post-stroke population that is cognitively able. Extension of the present study to less cognitively able patients will be important in clarifying this issue.

Dunbar et al. (2000) also conducted a factorial analysis of the HADS based on Clark and Watson's (1991) tripartite theory of anxiety and depression [20] [21]. This comprises factors believed to contribute to anxiety and depression, but sets these within a context of more generalised negative affectivity. Three factors linked to the HADS were also identified in this study, with similar implications for specificity. As previously noted, the present study data implies good specificity for the HADS in relation to anxiety and depression. This may reflect the different age cohorts used by Dunbar et al., (2000) described as "approximately 18, 39 and 58 years". Again, extension of the present study into younger age ranges may clarify this issue [21].

Limitations

Although attaining statistical power, the sample size in the present study is smaller than that suggested by prognostic calculations, which indicated each group should have n≥21. This reflects the large effect size found in all ANOVA's. The prognostic power calculations were based on conservative estimates of effect size. This was deemed appropriate given the lack of reference studies available regarding the GAI and GDS-SF for this population.

In terms of analysis, the key question is whether a questionnaire can identify the presence or absence of an index condition. Both index conditions are known to co-exist, so the overlap between groups does not necessarily invalidate the findings. Co-existence of anxiety and depression may be a

more accurate analogue of clinical experience, and the focus of this study is clinical utility. However, the findings of the present study would be more robust if a larger pool of participants had been studied, and if analyses were based on non-overlapping groups. This could be achieved in future by expanding the range of referrer sites and collecting data simultaneously across them.

Similarly, the participants are drawn from a convenience sample of people resident on rehabilitation wards or attending out-patient clinics. As such, the study has not accessed the population of stroke survivors receiving rehabilitative input in the community without regularly attending clinics. For instance, there are three Community Stroke Teams in Greater Glasgow which offer community based rehabilitation to stroke survivors. Patients in receipt of such home based rehabilitation were not included in this study. This is a limitation predicated on resources and safety policies for doctoral researchers that preclude participant contact outside of clinical settings. This could be rectified in studies operating under different constraints.

Generally, recruitment proved slower than anticipated, with the availability of suitable participants also varying across the duration of the study. In an attempt to address the unreliability of participant referral flow the researcher switched from a sequential “site by site” program of recruitment to simultaneous recruitment across multiple sites. This alleviated the problem somewhat, although it was still vulnerable to fluctuations in participant availability and the overall low availability of suitable participants. Given the Ethics Committee’s requirement that the initial approach to potential participants was not made by the researcher, there is no data on differences on opt-in to the study based on level of disability, gender, age, social background and mental health status. This means that the study sample may not be truly representative of the wider population under consideration.

Limited resources associated with doctoral training also contributed to a potential problem with blinding, in that all research protocols were carried out by one researcher. Standard 11 in the Standards for the Reporting of Diagnostic Accuracy Studies [STARD] Guidelines asks researchers to make explicit the qualifications of the researcher and flag up potential loss of blinding [36]. The present study did this, and also took steps to minimise loss of blinding. All MINI's were marked up during the minimum 30-minute break *before* participants were asked to complete questionnaires. Participants were required to complete questionnaires independent of the researcher. Consideration was also given to asking ward or clinic staff to administer the questionnaire measures, but this was felt to be an unrealistic expectation. Finally, the researcher had no vested interest in any of the measures assessed in the study, reducing the risks associated with loss of blinding.

Although the study was open to people aged 45 or over, only 12% (n=4) were 45-55 years old. 88% (n=30) were over 60. This does reflect local demographics of stroke, but does not meet the aims of the study and limits how much may be generalised from it. Further research will be required to provide robust scale validation data for GAI and GDS stroke survivors under aged 60 years.

Cognitive ability was not formally measured as it was felt to be onerous on participants. However, the clinical judgement of involved staff was solicited in terms of exclusion criteria. Therefore, the sample may be regarded as relatively cognitively able. This sample may not be representative of the wider post-stroke population however, particularly in early stages of rehabilitation. Saxena et al. (2008) note that "dementia and cognitive impairments occur in 17-65% of stroke patients" [37]. This means that the findings of the present study may be regarded as applying only to those who retain relatively high cognitive ability following stroke. It may, however, be argued that these are the patients most likely to be considered for questionnaire assessment.

Creed et al. (2004) make the point that screening for mood disorders following stroke often neglects those who have communication difficulties [38]. Verbal and/or visual administration of measures is indicated as good practice. As a third of people develop aphasia following stroke [39], this is a real concern. The present study was constrained by concerns about blinding, so could not offer verbal or visual administration of questionnaires. Studies with larger research teams will be best placed to overcome this limitation.

Conclusion

Based on the present findings, the GAI, GDS-SF and HADS are all able to distinguish stroke rehabilitation patients with index mood disorders from those without. This should be regarded in the context of a sample with relatively intact cognitive and communicative function. Closer examination of sensitivity and specificity data for the measures favours the HADS for clinical use in screening for both anxiety and depression in similar populations. The HADS is arguably briefer than the GAI or GDS-SF despite its more complex structure, and provides a robust measure for both anxiety and depression. The present study was not able to assess the measures with a less cognitively able sample, and such research might clarify concerns raised in the literature about lack of specificity and ease of completion.

The GAI is also an acceptable screening measure for anxiety for this population, but may prove more useful for patients with lower levels of cognitive functioning, or who would benefit from communication supported, for example, by dichotomous choice cards. Again, further research with such a population would be useful. It is unfortunate that the GAI does not appear to offer a highly robust anxiety measure for research in this population, as this is an area which appears currently under-researched.

The GDS-SF does not have sufficient sensitivity to be useful for the study population. There are measures which perform better, such as the HADS or the larger 30-item GDS-SF. Again, the dichotomous response format of the GDS may make it more suitable for those with cognitive or communicative difficulties. Further research to address this issue will also be required.

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Appendix 1

Author's notes for Stroke

Instructions for New Submissions

The following items should be uploaded with the manuscripts file(s).
A cover letter that includes the following statement, “All authors have read and approved the submitted manuscript, the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract (if relevant)”. The cover letter may include the names of up to 4 potential reviewers whom the authors would like to suggest, especially members of the editorial board. The authors may also include the names of up to 4 reviewers whom they would like to not evaluate their submission.
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Only Microsoft Word files will be accepted for review.
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Manuscripts should be presented in the following sequence; 1. Title page, 2. Abstract, 3. Text including Introduction, Methods, Results, Discussion and Summary/Conclusions, 4. Acknowledgments, 5. Sources of Funding, 6. Conflict(s) of Interest/Disclosure(s), 7. References, 8. Figure Legends, 9. Tables, and 10. Figures.
Cite each reference in text in numerical order and list in the References section. In text, reference numbers may be repeated but not omitted. Do not duplicate references either in text or in the reference list.
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Consult the AMA Manual of Style: A Guide for Authors and Editors, 10th ed, Oxford: Oxford University Press; 2007, for style.
Please provide sex-specific and/or racial/ethnic-specific data, when appropriate, in describing outcomes of epidemiologic analyses or clinical trials; or specifically state that no sex-based or racial/ethnic-based differences were present. See the Uniform Requirements for more details.

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Specify the number of words on your title page. Word count should include all parts of the manuscript (i.e., title page, abstract, main body of text, acknowledgments, sources of funding, disclosures, references, figure legends, and tables). Over-length manuscripts will NOT be accepted for publication without an additional page charge.

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Do not cite references in the abstract.
Limit use of acronyms and abbreviations.
Be concise (250 words, maximum). The abstract should have the following headings: Background and Purpose (description of rationale for study), Methods (brief description of methods), Results (presentation of significant results), and Conclusions (succinct statement of data interpretation). When applicable, include a fifth heading: "Clinical Trial Registration Information". Please list the URL, as well as the Unique Identifier, for the publicly accessible website on which the trial is registered.

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Follow the instructions in "Manuscript Formatting."
The following are typical main headings: Materials and Methods, Results, Discussion, and Summary.
Abbreviations must be defined at first mention in the text, tables, and figures.
Introduction section. This section should briefly introduce the context of the results to be presented and should duplicate what is contained elsewhere in the manuscript
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Prevention of bias is important for experimental stroke research (see Macleod et al, Stroke. 2009;40:e50-e52). For studies where the primary objective is the preclinical testing of therapies, the following checklist items must be adhered to.
Animals: Species, strains and sources must be defined. For genetically modified animals, wildtype controls including background and back-crossing must be defined.
Statistics and sample size: Specific statistical methods must be defined, including parametric versus nonparametric and multigroup analyses, and sample size powering based on expected variances and differences between groups.
Inclusions and exclusions: Specific criteria for inclusions and exclusions must be specified. For example, only animals where blood flow reductions fall below a certain threshold are included. Or only animals with a certain degree of neurological deficits are included. Once animals are randomized (see below), all excluded animals must be reported, including explicit presentation of mortality rates.
Randomization, allocation concealment and blinding: All animals must be randomized. Investigators responsible for surgical procedures or drug treatments must be blinded. End point assessments must be performed by investigators blinded to the groups for which each animal is assigned.
Results SectionThis section should succinctly report the results of experimental studies and clinical research or clinical series/observations.
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Reporting issues
Report process for selecting genes and SNPs.
Report Hardy-Weinberg statistics or P values and method of calculating same.
Refer to existing public domain websites for the Human Gene Ontology name and the rs number for SNPs.
http://www.gene.ucl.ac.uk/nomenclature/
http://www.ncbi.nlm.nih.gov/projects/SNP/
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Snp

Describe genotyping methods. If numerous primers have been used, please include them in an online supplement.
False-positive and false-negative concerns. Given well-described problems with both false-positive and false-negative associations, phenotype-genotype association studies should meet some or all of the criteria below:
Phenotype is clearly defined, is heritable, and if a quantitative phenotype is reported, reproducibility data are provided.
The sample size is adequate to detect a SNP or haplotype with a modest effect. For genotype-trait associations, provide an estimate of the effect size that could be detected with power 0.80 or higher with the allele frequency and sample size reported.
Since multiple statistical testing methods are frequently used in genotyping-phenotyping studies, please include specifics of the primary model(s) tested. Nonessential secondary models may be published as electronic data supplements. Clinically relevant confounders should be included in multivariable models or residuals.
Review criteria for human linkage studies. Manuscripts should include the following:
Identifying plausible candidate genes under the linkage peak.
Follow-up fine mapping to narrow the region of linkage, and/or genotyping some of the candidate genes under the linkage peak.
Replication data from another sample.
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Research is considered to be a clinical trial if it involves prospective assignment of human subjects to an intervention or comparison group to study the relation between a health-related intervention and a health outcome. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. As previously, purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration. Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration if they wish to seek publication.
The registry must be accessible to the public at no charge, searchable, open to all prospective registrants, and managed by a not-for-profit organization. The registry must include the following information: a unique identifying number, a statement of the intervention(s), study hypothesis, definition of primary and secondary outcome measurements, eligibility criteria, target number of subjects, funding source, contact information for the principal investigator, and key dates (registration date, start date, and completion date). The registries listed below are approved by the ICMJE:
United States National Library of Medicine
International Standard Randomized Controlled Trial Number (ISRCTN)

University Hospital Medical Information Network (UMIN)
Australian Clinical Trials Registry (ACTR)
Netherlands Trial Register

Clinical trials maybe listed with Other registries, but these registries must meet the above-mentioned requirements.
The authors will be requested to provide the exact URL and unique identification number for the trial registration at the time of submission. This information will be published in a footnote on the first page of the article.
Clinical trial reports should also comply with the Consolidated Standards of Reporting Trials (CONSORT) and include a flow diagram presenting the enrollment, intervention allocation, follow-up, and data analysis with number of subjects for each. Please also refer specifically to the CONSORT Checklist of items to include when reporting a randomized clinical trial.
Results posted in the same clinical trials registry in which the primary registration resides will not be considered prior publication if they are presented in the form of a brief abstract (<500 words or less) or a table.

Appendix 2.1

Major Research Project Proposal

Self Report Questionnaire Assessment of Anxiety and Depression amongst Stroke Patients in Rehabilitation Settings

Abstract

Background: Depression and anxiety are common sequelae of stroke, and can be detrimental to outcomes if not detected and addressed. The early stage of rehabilitation seems a natural point at which to undertake at least initial screening for depression and anxiety. Some existing self-report measures of anxiety and depression post-stroke have been criticised for lack of specificity and face validity of item structure [Hospital Anxiety and Depression Scale - HADS] or may not be fully validated for this population [Geriatric Depression Scale Short Form - GDS-SF]. A newly developed measure of anxiety may useful for this population [Geriatric Anxiety Inventory - GAI].

Aims: To assess the diagnostic utility of the HADS, GAI and GDS-SF against an interview based "gold standard" - the Mini International Neuropsychiatric Interview [MINI].

Methods: The administration of all four measures (GAI, GDS-SF, HADS, MINI) within a single sample of patients in rehabilitation following stroke.

Applications: Data on the structure, ease of use, sensitivity and specificity of the self-report measures (GAI, GDS-SF, HADS) for a stroke rehabilitation population may indicate the most clinically useful measures. Should GAI appear an acceptably specific and sensitive measure of anxiety it may also be useful to further research.

Introduction

Background

Stroke is an umbrella term for loss of oxygenated blood supply to one or more brain areas, typically causing impairment associated with the functions supported by the affected areas. This impairment must last over 24 hours and can be cognitive, emotional or physical in nature. The Information Services Division in Scotland [ISD Scotland] reports rates of incidence for Cerebrovascular Disease [CVD] which highlight that stroke is much more common in an older population, with incidence rising sharply beyond the age of 45. In 2007-2008 the overall incidence for both sexes in the 0-44 age range was 584. In the same period the incidence for people in the 45-64 age range was 2526. For the 65-74 age range the incidence was 2580. (ISD Scotland, 2009)

Depression and anxiety have been identified as common sequelae of stroke (Annoni et al, 2006). Hackett et al (2004) note that although depression may influence recovery and outcome following stroke, many, perhaps most, patients do not receive effective treatment because their mood disorder is undiagnosed or inadequately treated. There is therefore widespread agreement that early recognition and active management of post-stroke mood disorder is desirable (Thomas and Lincoln 2006). Research on post-stroke mood disorder has largely focussed on depression, perhaps reflecting a well studied correlation between depression and poorer outcomes including increased mortality (Salter et al, 2007). It may also reflect the hierarchical approach to psychiatric classification, in which anxiety diagnoses are subsumed by depression diagnoses (Burvill et al, 1995). However, Thompson (2000) notes that anxiety also can impede engagement and motivation in the context of stroke rehabilitation. This is supported by findings from studies exploring prevalence (Burvill et al, 1995; Astrom, 1996) which suggest that Generalised Anxiety Disorder [GAD] and Agoraphobia may be the most common anxiety disorders following stroke.

Scottish Intercollegiate Guidelines Network [SIGN] Guideline 64 (2002) “Management of Patients With Stroke” notes that stroke patients are at risk of treatable mood disorders and that screening

assessment plus follow up assessment through the course of rehabilitation is indicated. Self-report questionnaire measures can provide a quick way to carry out initial screening for mood disorders and therefore provide direction to appropriate treatment if required. However, although some reviews of such measures have found them acceptable (Berg, 2009) others have found their usefulness to be constrained by poor specificity (Lincoln et al., 2003).

The proposed research area is the clinical utility of the Hospital Anxiety and Depression Scale[HADS] for assessing both anxiety and depression, the Geriatric Anxiety Inventory [GAI] (Pachana et al., 2007) for assessing anxiety and the Geriatric Depression Scale – Short Form [GDS-SF] (Yesavage et al., 1983) for assessing depression in patients aged 45 or over following a stroke.

Two studies (Aben et al 2002, O'Rourke et al, 1998) have suggested that the Hospital Anxiety and Depression Scale [HADS] (Zigmond and Snaith, 1983) is a valid measure of mood disorder, including anxiety, in people who have had a stroke. However, there are several indicators that the HADS, although acceptable, might not be optimal for use with a stroke population. The HADS, despite being created for an unwell population contains some somatic items (e.g. "I feel as if I am slowed down") that may be over endorsed amongst a stroke population and has a 4-choice response format that is more complex than other measures with just a 2-choice response format. A literature review of HADS-based studies (Bjelland et al, 2002) noted that although it performed well as a bi-dimensional test (anxiety and depression) there was overlap between items and that optimal cut-offs varied across populations. This in itself may not be problematic: Carr (2006) notes "anxiety and apprehension" as clinical features of depression. However, a factor analysis of the HADS in relation to patients with Acquired Brain Injury [ABI], including stroke, found a three factor structure with the third factor not mapping well onto anxiety or depression (Dawkins et al., 2006). That is, HADS appears to be sensitive to a factor in ABI patients which is neither anxiety nor depression.

The GAI (Pachana et al., 2007) was developed as a measure of anxious cognitions in geriatric populations. The authors demonstrated its effectiveness in detecting GAD in this population (Sensitivity 75%, Specificity 84%). The GAI was specifically designed to be suitable for the over-60 population. Design features include brevity (20 items), dichotomous response format and less reliance on potentially misleading somatic symptoms. These features may also be helpful in assessing patients of any age who have had a stroke. It is as yet untested with a stroke population. Indeed, there seem to be few measures of anxiety that have been validated for post-stroke populations. This could be both a cause and effect of the relative rarity of research in this area.

The GDS-SF (Yesavage et al., 1983) is a 15 item questionnaire with a dichotomous response format. It is drawn from a longer 30 item version – the Geriatric Depression Scale [GDS]. On a preliminary literature search there are no validation studies for the 15 item version in stroke populations.

There is some support for the use of the 30 item GDS with stroke populations. Agrell et al (1989) found the GDS to perform acceptably for a stroke population in a range of settings (rehabilitation, day outpatient and nursing home) with a cut-off of 10/11 (Sensitivity 88%, Specificity 64%, PPV 58%, NPV 88%). Johnson et al (1995) found that a GDS cut-off of 10/11 yielded acceptable performance for detecting depression in a community based sample (Sensitivity 84%, Specificity 66%, PPV 53%, NPV 90%). Interestingly, they also assessed the performance of the GDS in detecting anxiety although it was not designed for this purpose. They found that with a cut-off of 14/15 it was also somewhat able to detect anxiety disorders (Sensitivity 65%, Specificity 79%, PPV 51%, NPV 86%). A study of depression measures in Chinese stroke patients in a rehabilitation hospital also found both the GDS and HADS performed “acceptably” but emphasised the need to consider cultural factors in

applying the evidence base for clinical use (Tang et al., 2004). As such, the findings of this study may not be applicable to a more Western population.

Thus, there is a modest evidence base for the use of the 30 item GDS with stroke patients undergoing rehabilitation. The evidence supporting use of the 15 item version with patients who have some degree of cognitive impairment is more mixed and does not directly address a stroke population. Friedman et al (2005) found it to perform acceptably in detecting depression among a functionally impaired but cognitively intact older population. Burke et al. (1991) found it to compare acceptably with the 30 item version in a cognitively intact population, but performed less well amongst patients with mild Alzheimer type dementia. Lesher et al. (1994) found both versions to perform acceptably in patients with a range of presentations - depression, thought disorder and dementia. Anecdotal report suggests that the GDS-SF is frequently used in stroke populations despite not being clearly validated for this purpose. This highlights the importance of investigating the validity of this measure for stroke patients.

There are several design features of both the GAI and GDS-SF that suggest the potential for their enhanced utilty in an older stroke population. If they are found to perform as well as or better than the HADS, such design features may suggest they would be a better choice of measure in patients with stroke. Both the GAI and GDS-SF are specifically designed for use with an older population, which reflects the demographics of stroke well. In terms of specificity, questionnaires designed around a single presenting complaint may be expected to perform better. Although less brief than the HADS, the GAI and GDS-SF are purposely brief measures, limiting participant fatigue (GAI is 20 items, GDS-SF is 15 items - compared to 7 items each for HADS anxiety and depression sub-scales). A particular strength may the dichotomous response format of both GAI and GDS-SF, which is likely to be less vulnerable to visuo-spatial disruption or cognitive difficulties than the 4-item response

format of the HADS. The GAI and GDS-SF also have less focus on potentially over-endorsed somatic symptoms than the HADS.

Aims

The present study aims to assess how suitable and useful the HADS, GAI, GDS-SF are in assessing anxiety and depression following stroke. Sensitivity and specificity data will be reported for all measures. A brief evaluation of each measure's acceptability (from the patient's point of view) will also be included.

For clinical use as a first stage screen it may be argued that sensitivity is more important than specificity – further investigation can tease out diagnoses. Given this, and the findings of the previously discussed research on the HADS, GAI and GDS, the present study will regard Sensitivity ≥ 75% and Specificity ≥ 65% as benchmarks for clinical utility.

Practical Applications

The present study would provide more information on the suitability of the HADS for a stroke population. If the GAI and GDS-SF are found to be suitable for detecting mood disorders in a stroke rehabilitation population it will provide clinicians with an alternative to the HADS for this population that may be preferable for some of the pragmatic reasons outlined previously, being potentially easier to complete and less vulnerable to over-endorsement of somatic items.

Primary Research Questions:

Will the GAI successfully distinguish those who meet DSM-IV criteria for an anxiety disorder from those who do not?

Will the GDS-SF successfully distinguish those who meet DSM-IV criteria for a depressive disorder from those who do not?

Will the HAD successfully distinguish those who meet DSM-IV criteria for an anxiety disorder from those who do not?

Will the HAD successfully distinguish those who meet DSM-IV criteria for a depressive disorder from those who do not?

Does the GAI have sufficient sensitivity and specificity to make it a useful clinical assessment tool for anxiety following stroke?

Does the GDS-SF have sufficient sensitivity and specificity to make it a useful clinical assessment tool for depression following stroke?

Does the HAD have sufficient sensitivity and specificity to make it a useful clinical assessment tool for anxiety following stroke?

Does the HAD have sufficient sensitivity and specificity to make it a useful clinical assessment tool for depression following stroke?

Hypotheses

Participants meeting a DSM-IV anxiety disorder criteria will have higher scores on the GAI than those who do not, at a statistically significant level ($p \leq 0.05$)

Participants meeting a DSM-IV depressive disorder criteria will have higher scores on the GDS-SF than those who do not, at a statistically significant level ($p \leq 0.05$)

Participants meeting a DSM-IV depressive disorder criteria will have higher scores on the HADS-D than those who do not, at a statistically significant level ($p \leq 0.05$)

Participants meeting a DSM-IV depressive disorder criteria will have higher scores on the HADS-D than those who do not, at a statistically significant level ($p \leq 0.05$)

The GAI will detect anxiety disorders with a sensitivity of ≥ 75% and a specificity of ≥ 65%

The GDS-SF will detect depression with a sensitivity of ≥ 75% and a specificity of ≥ 65%

The HADS anxiety sub-scale will offer equivalent sensitivity but inferior specificity to the GAI.

The HADS depression sub-scale will offer equivalent sensitivity but inferior specificity to the GDS-SF.

Method

Participants and Recruitment Procedures

Two main recruitment routes will be used, simultaneously. Firstly, potential participants engaged in ward or community based rehabilitation will be sought, either via ward staff or community working clinicians. The clinicians will be provided with information regarding the study, its inclusion and exclusion criteria, and will be asked to consider each potential patient's capacity to consent to participate in research. Potential participants considered to have capacity to consent will be provided with an information sheet regarding the study, inviting them to consider participation. The sheet will also discuss consent and the right to withdraw at any time. Participants will be asked to confirm to ward staff or community clinicians whether they would like to participate and then will the researcher be informed. If potential participants have not responded within 1 week, they will be asked by ward staff/clinician whether they would like to participate. If at this stage they are undecided or if they decline to take part no further reminders will be given.

A second tranche of potential participants will be identified following their admission to an Acute Stroke Unit. At the point of discharge they will be given an information sheet regarding the study. This will ask them to consider participation when attending for their standard Out-Patient Review in 3 months. The three month time lag between first contact and subsequent request for involvement is predicated by the organisation of services. Patients then attending for Out-patient Review who are judged to have capacity to consent will be reminded of basic information regarding the study and asked if they are interested in participating and if so the researcher will be informed. The research interview will take place immediately after their Out-Patient Review, in a nearby room.

Patients from both groups who express an interest in participation will be given the opportunity to ask the researcher further questions about participation and written consent solicited shortly

before procedures begin. Assessing consecutive patients prospectively over a fixed time period should provide the most naturalistic initial sample.

Settings

Interviews and assessments will be administered in a suitable room attached to or nearby the relevant ward or in another clinical setting (e.g. Health Centre) convenient to the community sample, if required.

Inclusion and Exclusion Criteria

Exclusion criteria:

Motor conditions severely affecting communication (e.g. dysarthria, apraxia of speech), cognitive communication difficulties (e.g. aphasia), psychosis, recent history of serious substance misuse or lack of capacity to consent.

Inclusion criteria:

Adults aged 45 or over in a period of rehabilitation following a stroke will be sought. All of the above exclusion criteria will have been assessed as routine by involved stroke clinicians. Therefore, only those participants deemed by a stroke clinician to have sufficient capacity to provide consent and to participate in research will be entered in the study. Should the researcher encounter evidence during the study that a participant's capacity may be questionable the researcher will seek immediate advice from a consultant clinical psychologist.

Creed et al. (2004) make the point that failure to administer measures such as the GDS to patients with dysphasia could lead to under-reporting of depression following stroke. They propose that using the GDS as a basis for a semi-structured interview may be a practical means of addressing communication difficulties in clinical use. The researcher did consider such an approach but administration of a psychiatric interview already forms part of this study. Therefore, further

interviewing seems inappropriate in terms of patient fatigue, duplication of effort and loss of blinding.

Design

Research Procedures and Equipment

Information on participants who consent to participate will be accessed from medical records resting with the relevant ward or service. This will include age, sex, general health history, mental health history, stroke and other neuro-pathological history.

Participants will be informed that reading is required in order to complete some measures and that a brief assessment of language ability will be administered first. They will also be advised that if the assessment suggests previously undetected language impairment the researcher will, with the participant's consent, pass this information on to ward or community staff depending on the setting.

Following Salter's (2006) review of post-stroke aphasia screening tools for use by those without expertise in Speech and Language Therapy, the Frenchay Aphasia Screening Test [FAST] (Enderby et al., 1987) will be used to assess linguistic ability. Salter reports that this measure has the most robust validation of those widely used, tests comprehension of written material and also benefits from brevity (5-10 minute completion). However, the focus of this will be ensuring that patients have sufficient reading ability to complete subsequent tasks. Relevant age-normed cut-offs will be applied. Those falling below cut-off will be thanked for their participation and advised that their participation has concluded.

For those scoring above the relevant cut-off, the researcher will then outline again what further participation will entail. If this is acceptable to the participant, the researcher will then briefly restate

their right to withdraw at any point and the limits of confidentiality. Participants will also be given leaflets covering these areas at the end of their participation.

Participation will be structured as follows. The Mini International Neuropsychiatric Interview [MINI] (Sheehan et al., 1998) will be administered to provide psychiatric diagnoses according to DSM-IV. The MINI is a semi-structured interview in which the assessor asks the patient directly about diagnostic criteria and follows a heuristic to generate diagnoses. It has been designed for quick administration, estimated at 15 minutes in a non-stroke population, reducing the risk of participant fatigue. It is, however, probable that administration time for the MINI will be longer for a stroke population. The MINI's authors found that its diagnostic utility compared favourably with other, more time consuming measures such as the Structured Clinical Interview for DSM-III, Patient Version [SCID-P] and Composite International Diagnostic Interview [CIDI] (Sheehan et al., 1998). Validation studies for the MINI are primarily by the authors apart from some studies validating non-English language versions. It was, however, the measure used in the development and validation of the GAI, and has been used in a validation study of the GDS-SF with cognitively intact but functionally impaired older people (Friedman etal., 2005). Pinninti et al. (2003) assessed the MINI as having good clinical utility and patient acceptability.

When assessed according to SCID-P diagnoses, Sheehan et al. (1997) found the MINI had good properties for detection of major depressive disorder (Sensitivity 0.96, Specificity 0.88, PPV 0.87, NPV 0.97) and for detection of current agoraphobia (Sensitivity 0.85, Specificity 0.88, PPV 0.69, NPV 0.95). Regarding reliability, the same study reports good reliability (kappa values) across 23 domains (inter-rater reliability ≥ 0.79 in all domains, test-retest reliability ≥ 0.75 in 14 domains). This, combined with the previously noted use of MINI in similar studies and support for its acceptability to patients, suggests that the MINI is likely to be suitable for the present study.

Following the MINI interview participants will be offered a 10-minute break to prevent fatigue. They will then be asked to complete the GAI, GDS-SF and HADS independently of the researcher and place them in an envelope. This is to ensure researcher blinding to participant self-report scores. The measures will not be titled (e.g. “Geriatric Anxiety Inventory”) in order to avoid priming. The self-report measures will be in large print to facilitate their completion. Similarly, large envelopes will be used to ensure participants do not experience undue difficulty in using them.

Qualitative measures of acceptability, such as semi-structured interview are most likely to be useful if conducted immediately following completion of each scale in order to maximise participant recall. In this case, however, their use seems inappropriate as they are likely to be onerous to patients and could compromise researcher blinding. Consistent with the previously stated rationale for use of a dichotomous response format, the two extra items below will be appended to each scale as a measure of acceptability.

1) Has this form been easy to complete? (Yes /No)
2) Has this form let you express your current state of mind? (Yes /No)

Measures

The principal measures in the study will be HADS scores, GAI score, GDS-SF score, ease-of-use endorsements and self-expression endorsements.

Other Data

Other data amenable to statistical analysis will be age, sex, neuro-pathological history, mental health history, Barthel & Rankin scores for functional adaptation (if available), handedness, deprivation category [DEPCAT] derived from post code.

Ethics

Access to patient records outwith clinical treatment will need approval from the Caldicott Guardian. Cognitive impairment raises questions about capacity to consent. Participants will be assessed for capacity to consent to participation in research prior to their consent being sought. The right to withdraw may also need extra emphasis. Participants may be more prone to fatigue and distress so pacing of tasks and regular checking of fatigue levels by the researcher will be required. Some participants may die from stroke or stroke related illness within the study's timescale.

As the researcher will not be offering any intervention to the participants, this will be made clear. If any of the measures employed indicate a psychological difficulty this information will be referred on to enable appropriate action to be taken. Under most circumstances this would be done with the patient's consent, but in the case of clearly expressed suicidal intent, information would be passed to an appropriate person without consent if necessary. This could mean sharing information with GPs, ward staff and Psychological Services. Participants will have to be made aware of this and the limits of confidentiality.

Health and Safety Issues

Researcher Safety Issues:

The main Health and Safety considerations will be around the potential for impulsivity, poor behavioural inhibition and emotional regulation in a stroke population.

Participant Safety Issues:

The main Health and Safety considerations will be around potential for fatigue and of distress caused by exploring negative affect in interview or questionnaire. There is also the possibility that a previously undetected mental health difficulty or risk factor (such as expressed intent to self-harm)

will emerge. It is believed that the design of the present study will adequately address the above these potential issues.

The ability of participants to consent and to safely participate will be assessed by a stroke clinician prior to them being invited to participate. All research procedures will take place within a clinical setting, with assistance readily available.

The measures and their administration are brief (estimated completion time is < 1 hour). A break is also planned to minimise patient fatigue.

The researcher will also give consideration to each participants' mood, behaviour and expressed experience of the procedure. The procedure will be suspended or ended if participants appear to be experiencing undue distress or high levels of agitation, with advice and assistance sought from relevant staff if significant distress persists for more than 3 minutes from suspension of procedures or if it rises to a level that suggests potential risk for the participant or researcher. The researcher's clinical judgement will be the main means of assessing levels of distress and risk. The researcher will therefore seek advice from experienced clinicians in regard to this before commencing any procedures.

Any psychological difficulties or additional risk factors detected during the procedure will be referred on appropriately to ward staff, GP or clinical psychology. Lines of communication for this purpose will be established prior to the commencement of the study, with advice from the researcher's field supervisor. Disclosure of difficulties to involved staff will, where possible, involve informing the participant of the researcher's intended action, the reasoning behind it and involving the participant in this process. Where this is not possible the reasons will be clearly recorded by the researcher.

For those settings without an integral alarm system a portable personal alarm will be used, and nearby staff informed.

Financial Issues

It is believed that the costs for the present study will be modest. Apart from the FAST, all proposed measures are paper based and free for research purposes. It is not envisaged that further specialist equipment or software will be required. Travel costs should be modest as most participants will be accessed at a limited number of locations within Greater Glasgow.

Data Analysis Procedures

Data analysis will be carried out using SPSS. Comparisons will be planned and, where relevant, predicated upon single-tailed hypotheses. Assumptions for parametric analyses seem likely to be met on testing.

Data will first be analysed to yield descriptive statistics for the sample and its sub-groups.

The DSM-IV diagnoses yielded by the MINI can be viewed as demarcating different groups within the sample – those who have current anxiety and / or depression disorders and those who do not.

ANOVAs will be used to explore differences in scores on the relevant measures (GAI,GDS-SF, HADS) between those who meet DSM-IV criteria for anxiety or depression disorders and those who do not. It is likely that some participants will meet criteria for both anxiety and depression disorders. In such cases the analyses will continue to be based on presence or absence of the currently considered index disorder (anxiety or depression). It is predicted that the disorder groups will have higher scores than the non-disorder groups.

Cronbach's Alpha will be used to assess internal consistency of the GAI, GDS-SF, HADS-A and HADS-D.

Pearson's *r* will be used to correlate participant scores on the GAI, GDS-SF, HADS-A and HADS-D.

Given concerns from the literature about the sensitivity and in particular specificity of measures this information will also be calculated and reported. Following Johnson et al's (1995) study, it may be instructive to assess the sensitivity and specificity of the anxiety measures for depression, and vice-versa. Data on sensitivity and specificity will also be used to tentatively suggest optimal cut-offs for each measure with this population. As indicated above, sensitivity will be prioritised over specificity.

Justification of Sample Size

Sample size and power calculations for ANOVAs were performed using G*Power 3.010 (Faul, Erdfelder et al, 2008) There is no existing data for effect size using GAI or GDS-SF in a stroke population. However, a large effect size (d = 1.2) can be calculated from data in the original validation study of the GAI (Pachana et al., 2007). For the GAI and GDS-SF to be clinically useful they will have to clearly distinguish those participants who meet DSM-IV criteria for anxiety or depression disorders and those who do not. This implies a large effect size (≥ 0.8). Based on this, to meet recommended statistical standards (power ≥ 0.8, $\alpha = 0.05$) G*Power suggests a sample size of 21 participants for each group.

Sample size and power calculations were calculated using an online calculator for Pearson's *r,* which will be used to examine the correlations between the measures of mood,. For a predicted correlation coefficient of 0.8 using statistical standards (beta ≤ 0.2, $\alpha = 0.05$) the calculator suggested a sample size of 8 participants for each group.

Sample size and power calculations for Cronbach's Alpha were performed using the trial version of Power Analysis and Sample Size [PASS] 2008 software. Cronbach's Alpha is sensitive to the number of items in a test – the fewer items in a test, the greater the number required in a sample to achieve adequate statistical power. In the present study, HADS-A and HADS-D have the fewest items of all

the tests (each having 7 items). Therefore, this value was used to determine the minimum sample size required where the Null Hypothesis Alpha value reflected no internal consistency (Alpha = 0.00) and the Alternate Hypothesis Alpha value reflected good internal consistency (0.80). To meet recommended statistical standards (power ≥ 0.8, $\alpha = 0.05$) PASS (2008) suggested a minimum sample size of 7.

The test most demanding of sample size is the ANOVA, requiring at least 21 participants for each potential group (Depressed, Anxious, Neither). The present study can be cautiously optimistic of recruiting sufficient numbers to achieve power from within the rehabilitation wards mentioned, and has also planned for accessing additional participants from wider community settings should this be required.

Expected Results

The HADS is already well-supported in the literature regarding other populations, albeit with some caveats. It is expected that this picture will be reflected in the present study of a post-stroke rehabilitation population. Given the face validity of the GAI's design features it seems likely that the GAI will be found to be acceptable to the stroke population. It may also be expected to perform adequately in the detecting the presence of anxiety disorders in this population. Specifically, the GAI is expected to closely match the MINI's diagnoses and correlate well with other measures (HADS). The literature around the GDS suggests that the GDS-SF may perform acceptably in detecting depression in stroke patients.

Timetable

c. August 2009 - Ethical approval sought

c. November 2009 – Data collection begins

c. April 2010 – Data collection ceases

c. April 2010 – Data analysis undertaken

c. May 2010 – Finalisation of Major Research Project begins

c. July 2010 – Submission of Loose Bound Clinical Research Portfolio

c. September 2010 – Viva

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Appendix 2.2

Participant Information Sheet

Participant Information Sheet

Assessing Mental Health following Stroke.

You are being invited to take part in a research project which is being run by the University of Glasgow Section of Psychological Medicine (Mr Blair Hanlon, Dr Niall Broomfield and Professor Jonathan Evans). Before you decide whether to take part, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information carefully. Talk to others about the project if you wish.

Please feel free to ask if there is anything that is not clear or if you would like more information (see contact details).

What is the purpose of the study?

The purpose of this study is to determine whether 3 different questionnaires are useful in detecting mental health conditions in people aged 45 and over who have had a stroke. The study is also part of Blair Hanlon's research work towards a Doctorate in Clinical Psychology.

It is important to note that not everybody will experience mental health conditions following stroke, but many people do. Mental health conditions can have a negative impact on recovery and rehabilitation following stroke. Identifying those people who have mental health conditions makes it easier to ensure appropriate care, and therefore aids recovery and rehabilitation.

Some previous studies have found short questionnaires to be a good way of checking for mental health conditions. However, it is less clear if they are suitable for people who have had a stroke. Therefore, this study will check if 3 carefully selected questionnaires are useful for people who have had a stroke.

There is no treatment involved in the study and there is no direct benefit to participants. Participants will, however, contribute to the identification of appropriate measures that may be of use to patients and professionals in the future. If evidence of a previously undetected mental health condition is discovered, appropriate referral onwards will be discussed with you. It is not believed that there is any physical risk associated with participation this study. Participants may experience emotional discomfort in discussing mental health conditions.

Why have I been asked to take part?

You have been asked to take part in this project because you have had a stroke and are at least 45 years old. Even if you feel you do not experience any mental health condition you can still take part.

For the study to be successful, we need a range of people with different experiences of mental health.

Do I have to take part?

No. It is up to you to decide whether or not to participate in this project. You will be asked to sign a consent form should you agree to take part in the project. You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

What do I have to do?

If you agree to be in this study, you will be asked to do the following:

The study will involve meeting with the researcher, Blair Hanlon, on one occasion, lasting approximately 60-90 minutes. This will be at a medical setting agreed by the researcher and you – for example at your hospital ward, outpatient department or a nearby health centre.

Participating in the study will require you to:

1. Complete a brief test of language use. (Approx. 15 mins)

If this is satisfactory you will then be asked to complete the next stages:

2. Respond to a brief interview about mental health conditions. (Approx. 20 mins)

You will then be offered a 10 minute break before the final element:

3. Privately complete 3 brief tick-box questionnaires about mental health conditions (Approximately 15 minutes)

Will my taking part in the study be kept confidential?

In brief, all individual responses will be treated as confidential. Ethical and legal practice will be followed and all information about you will be handled in confidence.

Your name will never be connected to your results or to your responses on the questionnaires. Instead, a number will be used for identification purposes. Information that would make it possible to identify you or any other participant will never be included in any sort of report. The data will be accessible only to those working on the project. The written document based on the project will not include information that could identify you or any other participant. This document will be assessed by staff from the University of Glasgow and may also be submitted for publication in relevant professional journals.

The results from the study will be written up for publication in scientific journals. All information in project reports is anonymised so that you could not be personally identified.

If any of the information gathered as part of the study may be helpful for the clinical team who are treating you then, if you would like us to, we can pass on the information to the clinical team.

Dr Niall Broomfield will have control of the data once the project is completed, and it will be kept confidential.

Contact Details

If you have any further questions or require more information please contact the principal investigator, or other member of the project team. See details below:

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Appendix 2.3

Study Consent Form

University of Glasgow Section of Psychological Medicine

Subject number:

"Self Report Questionnaire Assessment of Anxiety and Depression amongst Stroke Patients in Rehabilitation Settings"

Consent Form

Please initial the BOX

I confirm that I have read and understand the information sheet dated 27-11-09 (version 2) for the above study and have had the opportunity to ask questions ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

I understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to have access to my records. ☐

I agree to take part in the above study ☐

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Name of Participant Date Signature

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Name of Researcher Date Signature

1 copy to the patient, 1 copy to the researcher, 1 Original for the patients' notes