



## A systematic review of anxiety interventions in stroke and acquired brain injury: Efficacy and trial design



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### ABSTRACT

**Objective:** There is little randomized controlled trial (RCT) evidence to guide treatment for anxiety after stroke. We systematically reviewed RCTs of anxiety interventions in acquired brain injury (ABI) conditions including stroke and traumatic brain injury (TBI) in order to summarize efficacy and key aspects of trial design to help guide future RCTs.

**Methods:** We searched the Cochrane trial register, Medline, Embase, PsychInfo and CINAHL systematically up to August 2017. Two independent reviewers systematically selected studies and extracted data. We summarized the effect size, key study characteristics and sources of potential bias in trial design.

**Results:** 14 studies (12 stroke; one stroke & TBI; one TBI) with 928 participants were included. Meta-analysis of five psychotherapy comparisons favoured intervention over control (standardized mean difference (SMD):  $-0.41$  [ $-0.79, -0.03$ ],  $I^2 = 28\%$ ); Overall effect size of pharmacotherapy comparisons favoured intervention over control (SMD:  $-2.12$  [ $-3.05, -1.18$ ],  $I^2 = 89\%$ ). One comparison of mixed pharmacotherapy and psychotherapy favoured intervention over usual care (SMD:  $-4.79$  [ $-5.87, -3.71$ ]). One comparison favoured forest therapy versus urban control (SMD:  $-2.00$  [ $-2.59, -1.41$ ]). All positive studies carried high or unclear risk of bias. Sample sizes were small in all included studies.

**Conclusions:** There is low quality evidence to suggest that psychotherapy and pharmacotherapy may be effective interventions in the treatment of anxiety after stroke based on underpowered studies that carried high risk of bias. Large-scale well-designed definitive trials are needed to establish whether pharmacological or psychotherapy works. Our review highlighted key considerations for investigators wishing to design high quality trials to evaluate treatments for anxiety after stroke.

### 1. Introduction

Anxiety is a common neuropsychiatric complication of stroke with an estimated frequency between 20 and 25% [1]. There are two main subtypes of anxiety—phobic and generalized in non-stroke populations, requiring different treatment approaches. Phobic disorder is characterized by fear disproportionate to the threat posed by a well-defined situation, and marked avoidance of the situation [2]. Generalized anxiety disorder (GAD) presents with diffuse anxiety about events of daily life that is persistent and unremitting that the individual finds difficult to control [2]. In the general population, phobic disorder is treated with exposure techniques [3] whereas GAD responds to selective serotonin reuptake inhibitors (SSRI), short-term benzodiazepines and/or other cognitive behavioural therapy (CBT) techniques e.g. cognitive

restructuring, problem solving [4,5]. Randomized controlled trials (RCTs) of anxiety intervention in stroke have not yielded any definitive evidence in a recent Cochrane review—only three trials (2 pharmacological, 1 relaxation CD) with 196 participants were included [6]. These had high risk of bias and were of small sample size. Aware of the lack of RCT evidence in anxiety after stroke we aimed to review systematically the wider evidence base encompassing both stroke and traumatic brain injury (TBI). To date, there is no evidence to suggest that pathophysiological mechanism underlying anxiety disorders differs from one acquired brain injury (ABI) condition to another. The last systematic review of anxiety interventions in TBI in 2007 included three studies, providing some evidence for CBT in acute stress disorder, and in improving generalized anxiety symptomology but these studies had small sample sizes and were done in mild TBI only [7]. The current review

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would enable us to extrapolate from one ABI to the other as these conditions have abrupt onset, result in varying degrees of brain damage, and transient or long-term neurological and neuropsychiatric impairments. Furthermore, summarizing the key considerations in trial design (anxiety subtype targeted, setting and timing of intervention and outcome measure), and the sources of potential bias would help guide trialists to design high quality trials to evaluate anxiety treatments in the future.

### 1.1. Aims

To evaluate the efficacy of anxiety treatments and to summarize key aspects of trial design, we systematically reviewed RCTs of interventions—psychotherapy, pharmacotherapy or other types, for anxiety disorders in ABI conditions including stroke—*ischaemic*, haemorrhagic or subarachnoid haemorrhage (SAH), and TBI.

## 2. Methods

We followed a pre-defined protocol in conducting this systematic review and reported our review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [8].

### 2.1. Searches and information sources

We searched electronically for RCTs on Medline (1946-18/8/17), Embase (1980-17/8/17), PsychInfo (1940-17/8/17), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (inception-16/10/17), the Cochrane Stroke Register (16/10/17), and the Cochrane Central Register of Controlled Trials (CENTRAL) (inception-16/10/17) using search strategies supplied by the trials search co-ordinator of the Cochrane Stroke Group (Supplement B). We reviewed the reference list of key systematic reviews to date to identify additional titles [6,7]. We contacted authors of eligible titles that were trial protocols, conference abstracts or trial register entries for published or unpublished primary data.

### 2.2. Inclusion criteria

We included RCTs that evaluated interventions designed to target anxiety symptoms/anxiety disorder as a primary outcome, with any comparator group (placebo, usual care, waitlist control, active comparator). We included RCTs that recruited participants aged 18 or over with ABI conditions: *ischemic* or haemorrhagic stroke; SAH, confirmed by brain imaging with or without a lumbar puncture; moderate-to-severe TBI as defined according to the Scottish Intercollegiate Guidelines Network [9]. We excluded mild TBI, a clinical group that is difficult to diagnose reliably [10]. Where studies were carried out in a mixed sample, we included only those that recruited over 70% of stroke/SAH/moderate-to-severe TBI. We excluded trials that recruited exclusively military veterans. No language restrictions were applied.

### 2.3. Data collection

Two reviewers (HYC and RN) screened titles and abstracts independently and excluded ineligible titles. They assessed full text for eligibility and resolved discrepancies through discussion. A third reviewer (AJC) was consulted if a consensus could not be reached. They extracted data independently using an electronic data extraction form. HYC collated final data. One reviewer (HYC) assessed studies that were only available in Chinese.

### 2.4. Data extracted

We recorded key characteristics of the study population: ABI

diagnosis, age, sex, exclusion of specific deficit, baseline anxiety level, and intervention type (e.g. psychotherapy, pharmacotherapy, other).

#### 2.4.1. Quality assessment

We reported the level of bias across six domains of study design for the included studies: (A) random sequence generation, (B) allocation concealment, (C) blinding of participants and personnel, (D) blinding of outcome assessment (E) incomplete outcome data, and (F) selective reporting. We categorised the level of bias into 'low', 'high' or 'unclear' and recorded justification for our judgement for each domain in accordance with the Cochrane Risk of Bias Tool (<http://methods.cochrane.org/bias/assessing-risk-bias-included-studies>).

#### 2.4.2. Efficacy of intervention

We estimated effect size for each comparison by calculating the standardized mean difference (SMD) with 95% confidence intervals (CI) using the mean and standard deviation (SD) of the post-intervention anxiety severity. Meta-analysis was carried out for studies of the same intervention type using inverse variance and random-effects models. All analysis was performed using the Cochrane Review Manager (RevMan) Version 5.3 [11]. Where data were not reported in study publication we contacted the corresponding authors for further information.

#### 2.4.3. Key study characteristics and potential bias in trial design

We summarized the key study characteristics: anxiety type targeted, the setting and timing of intervention, outcome measures, the type of comparator, and ways that could have introduced or minimized potential bias in study design.

## 3. Results

The electronic searches yielded 8218 titles after removal of duplicates (Fig. 1). Of the 59 full text articles reviewed, we included 14 eligible studies with 928 participants. Sample size ranged from 17 to 206. Four studies were in Chinese [12–15]. No clear evidence of publication bias on funnel plot (Supplement C).

### 3.1. Characteristics of study population

Table 1 summarizes the characteristics of the 14 included studies. 12 studies recruited stroke patients only (*ischaemic* and primary haemorrhage) [12–23], one study recruited stroke and moderate-to-severe TBI [24], and one study recruited moderate-to-severe TBI only [25]. No study recruited patients with SAH. The mean age ranged from 48 to 72 years in studies of stroke patients only, and from 35 to 58 years in the two studies that included TBI patients. More men than women were recruited in all included studies. 12 studies excluded patients with communication difficulties due to aphasia or cognitive impairment [12–14,16–22,24,25]; one yoga exercise intervention excluded participants who were unable to ambulate independently [17]. Seven studies required participants to have a baseline diagnosis of anxiety disorder or 'emotional distress' either made on standardized diagnostic criteria e.g. Diagnostic Statistical Manual (DSM-IV TR), or by meeting a defined cut-off on a rating scale [12,13,19,22–25]. Six studies did not specify a baseline anxiety level for inclusion [14–18,20]. One study of a preventative intervention excluded the diagnosis of GAD on DSM-IV TR at baseline [21]. Studies used different anxiety rating scales at baseline and outcome assessment (Table 1): Hamilton Anxiety Rating Scale (HAMA) in five studies [12,13,15,21,23], Hospital Anxiety and Depression Scale-anxiety subscale (HADS-A) in three studies [19,20,25]; State-Trait Anxiety Inventory (STAI) in three studies [16–18]; Depression Anxiety Stress Scales (DASS) in one study [24]; Zung Self-rating Anxiety Scale (SAS) in one study [14]; Beck Anxiety Inventory (BAI) in one study [22].

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