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Maree L. Hackett, Maree L. Hackett, Sebastian Köhler, John T. O'Brien ...+2 more authors

**Institutions:** University of Central Lancashire, The George Institute for Global Health, Maastricht University, University of Cambridge ...+1 more institutions

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## Article

# Neuropsychiatric outcomes of stroke

Hackett, Maree L, Köhler, Sebastian, O'Brien, John T and Mead, Gillian E

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## **Neuropsychiatric consequences of stroke: a review**

Maree L Hackett PhD

Associate Professor, Head of Mental Health and Chronic Disease program, The George Institute for Global Health, The University of Sydney. Reader in Epidemiology, School of Health, The University of Central Lancashire, Preston, United Kingdom

Sebastian Köhler PhD

Research fellow, Alzheimer Centre Limburg, School for Mental Health and Neuroscience, Maastricht University, The Netherlands

John T O'Brien DM

Professor of Old Age Psychiatry, Department of Psychiatry, University of Cambridge and Cambridgeshire and Peterborough NHS Foundation Trust

Gillian E Mead FRCP

Professor of Stroke and Elderly Care Medicine, Geriatric Medicine; Centre for Clinical Brain Sciences and Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh

Key words

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## **Panel 1**

### **Search strategy (see appendix)**

## **Panel 2**

### **Areas for research**

Is there a common cause for neuropsychiatric consequences of stroke, which might explain the overlapping symptoms?

What factors are associated with anxiety, emotional lability and post stroke fatigue without mood disorder?

What is the natural course of post stroke anxiety and emotional lability?

How should post stroke depression, emotional lability, fatigue and apathy be treated (including dose and duration of treatment)?

Can these neuropsychiatric consequences of stroke be prevented by early intervention after stroke?

## **Abstract**

The most common neuropsychiatric consequences of stroke include depression, anxiety, fatigue and apathy, each occurring in at least 30% of patients, with considerable overlap of prevalence and symptoms. Emotional lability, personality change, psychosis and mania are less common but are equally distressing symptoms which are also challenging to manage. The cause of these syndromes is uncertain, and there is no clear relationship with brain lesion location. There are important gaps in our knowledge about how to manage them; even for depression which is the most well-studied syndrome. Further research is needed to identify causes, and interventions to prevent and treat these syndromes.

## **Introduction**

Each year, about 16 million people in the world experience a first-ever stroke. Of these about 5.7 million die and another 5 million remain disabled.<sup>1</sup> Neuropsychiatric consequences of stroke are common, can be distressing to patients and their families and often represent an unmet need for treatment.<sup>2</sup>

This review focuses on the most common non-cognitive neuropsychiatric consequences of stroke namely depression, anxiety, emotional lability and apathy; we also include fatigue (which is generally categorised as ‘neuropsychiatric’) and discuss personality change, psychosis and mania. For each consequence, we discuss definition and identification, prevalence, associations, natural history/outcome, prevention and treatment, based on our literature searches, then make recommendations for future research. Researchers have tended to consider each neuropsychiatric consequence separately, so we follow this same approach, acknowledging though that there is considerable overlap between the syndromes. We include intracerebral haemorrhage and ischaemic stroke. We did not specifically search for, or include papers focusing on transient ischaemic attacks or subarachnoid haemorrhage. We do not include dementia.

## **Our approach to the literature**

We searched Medline using the terms ‘stroke’, and each neuropsychiatric problem in turn, to identify systematic reviews and primary research (box). These searches complemented previous searches we had performed, and so Medline was not necessarily searched from its inception. We scrutinised the Cochrane Stroke Group list of reviews and the Royal College of Physicians (RCP) Guidelines for stroke (2012)<sup>3</sup> for which extensive literature searches had been performed. We screened reference lists of reviews. Our management recommendations

are based on data from randomised controlled trials (RCTs) or meta-analyses of RCTs but not from uncontrolled case series. In the absence of such data, we provide consensus recommendations.

## **Depression**

The US Diagnostic and Statistical Manual of Mental Disorders, DSM-5<sup>4</sup> requires ‘depressed mood’ *or* ‘anhedonia/loss of interest or pleasure’ for at least two weeks, plus at least four other symptoms which are persistent and interfere with daily life (‘significant weight loss/gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; worthlessness or inappropriate guilt; diminished concentration or indecisiveness’).

In busy and resource-poor clinical settings, it is often appropriate to first use an interviewer-administered or self-completed depression case-finding or screening tool, validated for use in stroke<sup>5</sup> (e.g. the 9-item Patient Health Questionnaire<sup>6</sup>, The Center of Epidemiological Studies-Depression Scale<sup>7</sup>, Hospital Anxiety and Depression Scale (HADS), the Hamilton Depression Rating Scale and the Beck Depression Inventory<sup>8</sup>).

When diagnosing depression, consideration may be given to ensure somatic symptoms such as psychomotor retardation, fatigue, sleep and appetite disturbances are related to mood, and not to the physical symptoms of stroke. However, this is difficult to implement in practice and there is evidence that psychomotor retardation and fatigue are highly sensitive for depression after stroke.<sup>9</sup> These symptoms are unpleasant and the clinical goal should be to reduce all unpleasant symptoms where possible. Equally important is the need to ensure that disturbances in behaviour, facial expression and verbal communication resulting from the stroke event do not mask symptoms of depression.

RCP guidelines<sup>3</sup> recommend that all stroke patients are screened for mood disorders within 6 weeks. However, such screening is only worthwhile if followed by a fuller clinical diagnostic

assessment and an agreed management plan.<sup>10</sup> Observer rated screening tools (e.g. Stroke Aphasic Depression Questionnaire<sup>11</sup> or The Depression Intensity Scale Circles<sup>12</sup>) can be used to identify mood disturbance in people with aphasia or other communication problems; however, as for other screening, clinical judgement is then needed to decide if the patient has depression and whether treatment is needed.

Depression occurs more frequently after stroke than in the general population. Data in two independent systematic reviews (43 cohorts, 20,293 people<sup>13</sup> and 51 cohorts including 25,207 people<sup>14</sup>; 21 cohorts included in both reviews) indicate that between 29%<sup>13</sup> and 33%<sup>14</sup> of stroke patients experience depression up to one year after stroke. Estimates from individual studies assessing *major* depression meeting DSM criteria varied across studies from 2% during admission<sup>15</sup> in one cohort to 31% at three months in a different cohort.<sup>16</sup> In the latter cohort, major depression meeting DSM criteria was assessed over three years. Estimates were 31% at three months, 16% at 1 year, 19% at 2 and 29% at three years after stroke (only 50 participants remained in the final cohort).<sup>16</sup>

Population based stroke registers with long-term follow-up<sup>17-19</sup> demonstrate that depression after stroke is a chronic relapsing disorder. Of people with depression at the first assessment, between 13%<sup>18</sup> and 52%<sup>19</sup> still had depression at a year. Approximately 15% of those without depression at initial assessment developed depression during the first year.<sup>17, 19</sup>

One systematic review of observational studies of depression after stroke (20 cohorts, n=17,934) indicates that only physical disability, stroke severity and cognitive impairment consistently show a positive association with depression (note that most included studies excluded people with pre-stroke depression).<sup>20</sup> A second independent review using different methods included 10 cohorts (n=16,045)<sup>13</sup> and identified pre-stroke depression as being associated with subsequent depression after stroke, in addition to disability, stroke severity, cognitive impairment. Variables not associated with depression include older age, being



female, having diabetes, stroke subtype, level of education, living alone or previous stroke.<sup>20</sup> Only one cohort was included in both reviews. Only a small proportion of the variation in depression was accounted for, though the included studies generally had sample sizes which were too small for multivariate analyses.

A Cochrane review of pharmacological or psychological interventions to prevent post-stroke depression identified 14 trials involving 1515 people<sup>21</sup>, and reported a small but significant effect for psychological interventions (of various types) (4 trials) but no evidence of effect of antidepressants (10 trials) (figure 1). Four small antidepressant trials<sup>22-25</sup> (384 people) potentially meeting Cochrane criteria have been published since the 2008 update, three<sup>22, 24, 25</sup> showed some evidence of benefit of antidepressants, though their inclusion in the Cochrane review is unlikely to significantly change overall estimates of effect.

A Cochrane review of pharmacological or psychological interventions to treat depression after stroke identified 16 trials recruiting 1655 people<sup>26</sup> (figure 1) and showed that antidepressants (13 trials) are minimally effective (no evidence of differences in efficacy between antidepressants) with an increase in gastrointestinal and central nervous system (e.g. confusion, sedation, tremor) side effects. This is in line with a systematic review of trials in the general population showing antidepressants are minimally effective for mild to moderate depression,<sup>27</sup> but of substantial benefit for severe depression. The Cochrane review found no evidence of effectiveness for psychological therapies alone (4 trials) in treating depression after stroke.<sup>26</sup> One small antidepressant treatment trial (150 people) possibly meeting review criteria was identified since this review and showed a small benefit of treatment.<sup>28</sup>

The United Kingdom Royal College of Physicians guidance is that support and advice is the first-line management for patients with mild or moderate symptoms of depression, and psychosocial interventions should be considered<sup>3</sup>. These guidelines also recommend increased social interaction, exercise and goal setting (though our searches found insufficient evidence

to support or refute their effectiveness).<sup>3</sup> The American<sup>29</sup> and European<sup>30</sup> guidelines recommend pharmaceutical treatment (Selective Serotonin Reuptake Inhibitors or heterocyclics) for patients with depression<sup>29, 30</sup>. The guidelines recommend that treatment should be monitored for effectiveness, and antidepressants (if used) continued for at least 6 months after initial recovery. The choice of antidepressants for individual antidepressants can be guided by side effect profile e.g. antidepressants with sedative properties may be appropriate in patients with disturbed sleep.

### **Anxiety**

The DSM-5<sup>4</sup> describes several anxiety disorders. Anxiety symptoms that are ‘out of proportion to the actual threat or danger the situation poses’, must be present for six months to meet diagnostic criteria for a Generalised Anxiety Disorder, plus at least three of the following symptoms: feeling wound-up, tense or restless; fatigued; difficulty concentrating; irritability; significant muscle tension; difficulty sleeping. To our knowledge, the HADS<sup>8</sup> is the only anxiety-specific case-finding tool validated for use in stroke research and clinical settings with published sensitivity and specificity data.<sup>31, 32</sup> If the HADS is used to screen for anxiety, then as with other screening tools clinical judgement is then needed to decide if the patient has clinically significant anxiety and whether treatment is needed.

A systematic review (39 cohorts including 4,706 people) indicated that 24% of stroke patients had anxiety symptoms as assessed by a rating scale, and 18% experienced an anxiety disorder, over the first five years after stroke.<sup>33</sup> In this review, three cohort studies (856 people) reported anxiety in individual participants over time; the proportion with persistent anxiety ranged from 38% to 76%.

Studies evaluating factors correlated with anxiety in more than five cohorts have been narratively (but not systematically) reviewed.<sup>33</sup> Depression was positively correlated with

anxiety in six of six cohorts and quality of life was negatively correlated with anxiety in four of five cohorts. No association was found with age, sex or brain lesion location. The factors associated with anxiety in people without depression after stroke are unknown.

There are no studies on anxiety prevention after stroke. A Cochrane review of interventions to treat anxiety after stroke identified two trials involving 175 people.<sup>34</sup> Both trials included people with co-morbid anxiety and depression and neither was placebo-controlled. Antidepressants alone or with psychotherapy may reduce anxiety symptoms but there is insufficient evidence from the Cochrane review to inform clinical practice.

### **Emotional lability**

Emotional lability is described as ‘unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense and/or out of proportion to events and circumstances’.<sup>4</sup> It is also referred to as emotionalism, pathological laughing/crying, emotional incontinence, involuntary emotional expression disorder and pseudobulbar affect. There is no standard method of assessment. It usually presents as an increase in crying or, less commonly, laughing, and may co-exist with depression or depressive symptoms but can occur without depression. Symptoms are generally mild and transient, but when severe can cause great distress, embarrassment and avoidance of social contact.

A few high quality studies reported that the frequency of emotional lability<sup>35-41</sup> varies across individual studies from 8%<sup>35</sup> at four months in one cohort to 32%<sup>37</sup> three to 12 months after stroke in another. Symptoms are thought to reduce over the six months following stroke.<sup>36</sup> The factors associated with reduction of symptoms are unknown.

There are no published systematic reviews of the associations of emotional lability after stroke. Most research has focused on biological explanations with an association between emotional

lability and frontal lesions found in four cohorts<sup>36, 41-43</sup> and an association with dorsal lesions in the other.<sup>44</sup>

A Cochrane review of pharmacological interventions to treat emotional lability after stroke (seven trials, 739 people, recruited at 6 days to 13 years after stroke) reported that antidepressants reduced its frequency and severity but confidence intervals were wide (figure 2).<sup>45</sup> It is reasonable to use antidepressants for persistent emotional lability that is frequent and severe enough to warrant the known risks of antidepressants<sup>3</sup>; but the optimum type, duration or dose is unknown.

### **Post-stroke Fatigue**

There is no standardised definition for post-stroke fatigue.<sup>46</sup> Physiological (or normal) fatigue (a state of general tiredness which develops acutely after overexertion and improves after rest) and pathological fatigue ('constant weariness unrelated to previous exertion levels and not usually ameliorated by rest').<sup>47</sup> tend to be distinguished in the literature, and in neurological diseases, 'pathological fatigue' is more prominent than 'physiological' fatigue.<sup>48</sup> Post-stroke fatigue can be identified using a self-report fatigue scale,<sup>46</sup> or by structured interview to establish fulfilment of a case definition (analogous to a structured interview to identify depression).<sup>47</sup> There is little empirical evidence to support the concepts of 'Primary', 'secondary', 'central' and 'peripheral' fatigue in stroke. The proportion of people with post-stroke fatigue ranges from 23% to 75%, according to case mix, and how fatigue is identified.

<sup>46</sup> Using a case definition, about 40% of stroke patients have fatigue.<sup>49</sup>

A systematic review of 9 longitudinal cohort studies (n=959) reported that the frequency of fatigue declined over time in seven studies (n=764) and increased in two studies (n=195).<sup>50</sup> Two subsequent studies reported that fatigue frequency was stable over time.<sup>51 52</sup>(table) Fatigue tends to persist in individual patients if present early after stroke.<sup>50</sup>

The nature of post-stroke fatigue is different from fatigue experienced before stroke<sup>53</sup> and it seems to start around the time of the stroke.<sup>54</sup> There is no clear association with brain lesion location<sup>55</sup>, little evidence about biological correlates.<sup>55</sup> and one study demonstrating associations with attentional deficits.<sup>51</sup> A literature review in 2011 reported associations with depression, pain and poor sleep.<sup>46</sup> Fatigue in conditions other than stroke is associated with reduced physical activity; whether this applies in stroke is uncertain.<sup>56</sup>

A Cochrane review of 3 small randomised trials (142 people) which included fatigue as an outcome measure found no effective preventative or treatment strategies.<sup>57</sup> One subsequent trial (n=83) without a control arm showed that treadmill aerobic training and cognitive behavioural therapy (CBT) together was better than CBT alone to treat post-stroke fatigue,<sup>58</sup> A small trial (n=19) demonstrated that group education was a feasible treatment.<sup>59</sup> Screening for fatigue is not currently recommended in guidelines. In patients with post-stroke fatigue, we suggest seeking potentially reversible causes e.g. anaemia, treating depression (if present), and in patients without patients without a clinical mood disorder or reversible medical problem, considering graduated exercise and cognitive behavioural approaches e.g. activity scheduling<sup>3</sup>.

## **Apathy**

Apathy is a disorder of motivation with diminished goal-directed behaviour and cognition<sup>60</sup> which has its own distinct biological correlates, clinical course and treatment. Nevertheless phenomenological overlap (e.g. affective blunting, loss of interest, psychomotor retardation) with depression can make differential diagnosis difficult.<sup>60</sup> Apathy can be identified by informant-rated scales e.g. Apathy Scale<sup>61</sup> or Apathy Evaluation Scale<sup>62</sup> ( designed and tested for use in brain-injured populations) or the generic Neuropsychiatric Inventory (NPI), also requiring an informant, which rates frequency and severity of several neuropsychiatric

symptoms (delusions, hallucinations, agitation, depression, anxiety, mood elation, apathy, disinhibition, irritability, aberrant motor behaviour, sleep, appetite).<sup>63</sup> Diagnostic criteria for apathy have recently been proposed,<sup>64</sup> requiring diminished motivation (core feature) for four weeks or more, two other symptoms (reduced goal-directed behavior, goal-directed cognitive activity, or emotions), and functional impairments. Symptoms and states that mimic apathy should be excluded. These criteria largely build on studies in apathy in dementia; whether they are appropriate for stroke is uncertain.

In a meta-analysis of 2,706 patients from 24 studies, the mean prevalence of apathy was 34.6% at a median of 120 days post stroke.<sup>65</sup> Another meta-analysis found similar figures.<sup>66</sup> Apathy is more common in women,<sup>65</sup> in studies using clinician-ratings compared to self-ratings or informant-ratings,<sup>65</sup> and in recurrent strokes.<sup>66</sup>

We identified three prospective studies (recruiting 408, 106 and 145 stroke patients), but methodological differences make direct comparisons difficult. The proportion whose apathy had remitted at follow-up ranged from 44%<sup>67</sup> to 67%<sup>68</sup>. The development of new apathy during follow-up occurred in only 7% of patients<sup>69</sup>.

In cross-sectional studies, apathy is associated with less education, cognitive impairment (particularly attention, concentration, working memory and reasoning)<sup>70</sup> and increasing disability.<sup>65, 66</sup> Depression co-occurs in about 40% of apathetic patients.<sup>65</sup> No convincing evidence links brain lesion location or stroke type to post-stroke apathy.<sup>65</sup> We identified one publication that studied risk factors for apathy prospectively; new incident apathy 15 months after stroke was predicted by a diagnosis of dementia three to six months after stroke, but not by age, gender, stroke severity, previous psychiatric history, current depressive symptoms, or living with a family member.<sup>67</sup> Apathy is associated with worse functional outcome,<sup>71-73</sup> and a higher risk of subsequent depression.<sup>67</sup>

There is insufficient evidence for treatment recommendations for post-stroke apathy. One RCT in 137 stroke patients with depression showed that 900mg/day nefiracetam for  $\geq 4$  weeks resulted in a greater change in scores of the Apathy Scale (secondary outcome) compared to 600mg and placebo.<sup>74</sup>

## **Mania**

Mania is defined as a prominent and persistently elevated, expansive or irritable mood, accompanied by changes in energy or activity, not accounted for by another mental disorders and not exclusively present in the course of delirium.<sup>4</sup> Accompanying symptoms include hyperactivity, pressured speech, flight of ideas, grandiosity, decreased sleep, distractibility, or lack of judgement. Symptoms have to cause significant distress or impairment in social, occupation or other important functions. The clinical profile in post-stroke mania is similar to that of primary mania.<sup>75, 76</sup> We identified three scales for rating the severity of manic symptoms<sup>35-37</sup> but no studies that have actually used these scales with stroke patients.

The literature on mania after stroke is meagre. Its prevalence is considered to be low ( $\leq 2\%$ ), yet good epidemiological data are lacking.<sup>70</sup> A systematic review of all studies published in the past 50 years identified 32 reports including only 49 patients, mostly gathered from single case or small case series reports.<sup>76</sup> Delirium as a potential cause was specified in only about half of patients and a medical doctor or psychologist had conducted the interview in a minority (22%). Onset in these 49 patients was generally reported to be insidious; about half develop manic symptoms within the first days after stroke and the rest 1 to 24 months after stroke.<sup>76</sup> The prevalence of single manic symptoms has been reported for euphoria/elated mood using the NPI; prevalence estimates range from 1% to 14%.<sup>68, 77-79</sup>

Our literature search identified no prospective studies on the course of mania after stroke, no studies reporting associations (other than the review of 49 individual cases which described the

typical patient as being male, having vascular risk factors and a lesion in the right hemisphere) and no trials of interventions for prevention or treatment. No conclusive associations have been found with single symptoms of euphoria/elated mood.

### **Personality disorders after stroke**

The DSM-V differentiates three clusters of Personality disorders .<sup>4</sup> In order to classify as personality disorder, the changes have to be long-standing and hence require long follow-up of individual patients. We are not aware of any such study in stroke. A cross-sectional survey in the UK reported personality disorders in 0.8% of individuals with stroke compared to 0.4% without stroke; it is unclear whether personality disorder might have preceded the stroke.<sup>80</sup>

### **Personality changes, including disinhibition and irritability**

Personality changes after stroke are not well defined and at times are used as an umbrella term for any neuropsychiatric syndrome, especially apathy.<sup>70</sup> Assessing change in personality can be challenging, because information on pre-stroke personality might not be available. The NPI asks informants to consider only changes in a patient's behaviour since illness onset. It includes questions on disinhibition and irritability, which are often classified as personality changes,<sup>81</sup> and are among the most distressing symptoms for carers and family members.<sup>82, 83</sup> Irritability is characterized by impatience, flashes of anger, rapid mood changes, or quarreling,<sup>79</sup> and disinhibition by impulsivity, tactlessness or – albeit less often – by vulgarity.<sup>79</sup>

Prevalence estimates for irritability vary from 12-53%.<sup>68, 77</sup> In a study of 274 institutionalized stroke patients, it was the more common (prevalence 52.9%) than depressive symptoms (52.6%) or apathy (34.3%).<sup>77</sup> It is more common in those with accompanying depression,<sup>84</sup> emotional lability,<sup>85</sup> and cognitive impairment.<sup>86</sup> Prevalence estimates for disinhibition vary



from 6-76%,<sup>78, 87</sup> partly due to differences in scales used and research setting (e.g. higher prevalence in acute hospital,<sup>87</sup> than rehabilitation center<sup>68</sup>).

Two studies of 11 and 49 affected patients respectively<sup>68, 88</sup> suggested that irritability tends to improve over time, and in one (n affected=10) disinhibition improved over time.<sup>68</sup>

Our searches identified several studies reporting associations with brain lesion location; there is no consistent association with disinhibition, irritability, or aggression<sup>77, 84, 87, 89-92</sup>. Irritability/aggression has been associated with higher overall psychopathology, depression and anxiety, and poor cognition.<sup>91</sup>

Our searches identified no clinical trials on the prevention or treatment of personality changes, disinhibition or irritability after stroke. In a post-hoc analysis of a double-blind randomized controlled trial for treatment of post-stroke depression, antidepressant treatment significantly reduced irritability symptoms.<sup>91</sup>

### **Psychosis and psychotic symptoms**

‘Psychosis’ refers to disorders involving a severe distortion in thought content. While it is commonly used for schizophrenia and related disorders, it also applies to mania and severe depression.<sup>93</sup> Single psychotic symptoms can also be due to other causes including delirium, dementia, or use of psychoactive drugs/dopamine agonists. The most prominent symptoms include delusions and hallucinations. Delusions are “erroneous beliefs that usually involve the misinterpretation of perceptions and experiences”.<sup>93</sup> Hallucinations are abnormal perceptions that are not experienced by others, which can occur in any modality and can be simple (e.g. light flashes, single sounds) or complex (e.g. seeing whole scenes, hearing voices, seeing objects in Lilliputian form (i.e. smaller than normal)).<sup>56</sup> Most research in stroke populations has

used the NPI, which includes two sections on the frequency and severity of any-type of delusions and hallucinations<sup>63</sup> rather than specific scales e.g. Positive and Negative Symptom Scale<sup>94</sup> and the Brief Psychotic Rating Scale.<sup>95</sup> There is no literature about which is the most appropriate scale to use in stroke.

Our literature search did not identify any high-quality epidemiological studies with active case ascertainment. Two hospital-registry studies identified only 0.4%<sup>96</sup> and 3.1%<sup>97</sup> of stroke patients with a psychotic disorder. The incidence was 1.11 per 1000 person-years, with gradual onset at an average of 6.1 months after stroke.<sup>97</sup> Single psychotic symptoms not fulfilling criteria for syndromal psychotic disorder appear more common. For example, among patients admitted to somatic or rehabilitation wards of Dutch nursing homes, delusional symptoms were present in 3-10% of patients<sup>68, 77</sup> and hallucinations in about 4%.<sup>68, 77</sup> Visual hallucinations are more common (12%) in patients with occipital strokes.<sup>98</sup> Auditory hallucinations were present in 4 out of 521 (0.8%) patients with cortical stroke,<sup>99</sup> though they might be more common in subcortical strokes.<sup>100</sup> Note that we cannot rule out the possibility that some of these patients may have had delirium as a cause of psychotic symptoms. There is insufficient information on lesion location or the outcome of psychosis and psychotic symptoms. In a retrospective cohort study of 1008 stroke patients, psychosis was the only neuropsychiatric disorder significantly associated with a higher mortality rate, but why this should be specific to psychosis is obscure.<sup>97</sup> No prospective studies on the course and outcome of post-stroke psychosis are available. No clinical trial reported on prevention or treatment of psychosis after stroke.

**Research directions** There is considerable overlap between each neuropsychiatric syndrome.. Depression frequently coexists with anxiety and emotional lability, fatigue is a symptom of depression and anxiety, apathy is associated with depression and cognitive impairment, and personality changes are associated with emotional lability, depression and

cognitive impairment. This raises the question about whether there are shared underlying mechanisms e.g. fluctuations in neurotransmitters, aspects of the inflammatory cascade, disrupted functional connectivity in the limbic system and inability to regulate arousal. Brain lesion location seems not to be associated with specific syndromes (except for visual hallucinations)

. There was a dearth of literature on apathy, even though it is reported to be as common as depression.

There are important knowledge gaps in relation to management. Even for depression there is no clear evidence about how to treat patients with mild to moderate post-stroke depression, and a dearth of evidence about how to manage people with suspected depression in whom mood cannot be formally assessed because of aphasia.

Further studies exploring the associations and outcome of these syndromes (particularly emotional lability, personality change, apathy and psychosis) are needed to identify associated factors that might be potential targets for prevention and treatment. Robustly designed prevention and treatment trials are needed for each of the syndromes, perhaps by adapting for interventions that have been used in other conditions. The trials we identified were generally small. Large, high-quality, well-powered trials are needed that will provide definitive answers about the effectiveness (or not) of interventions.

**Conflict of interest.** Prof Mead has received expenses to lecture on post-stroke fatigue at international meetings, honoraria to produce a module on exercise after stroke for the World Stroke Organisation, and royalties from Later Life Training, for provide teaching material on exercise after stroke. A/Prof Hackett has received expenses to lecture on post-stroke depression at international meetings. John O'Brien has received travel support and/or honoraria for non-promotional lectures from Pfizer, Eisai, Lundbeck, Novartis, Lilly and Shire and acted as a consultant for GE Healthcare, Bayer Healthcare, Lilly, TauRx and Cytex. Sebastian Köhler reports no conflicts of interest.

### **Role of the authors**

Maree Hackett performed the literature searches for the sections on depression, anxiety and emotional lability, and wrote these sections. Professor Mead performed the literature searches for fatigue. Sebastian Köhler performed the literature searches for the sections on apathy, mania, personality changes and psychosis and wrote the first draft of these sections. John O'Brien provided additional references. All authors commented on drafts of the paper, and all contributed equally to the final section on directions for future research. Permissions for the figures were obtained by Maree Hackett and Gillian Mead.

## Table

Summary of longitudinal studies of post-stroke fatigue, adapted from Journal of Psychosomatic Research

<b>Study</b>	<b>Assessment points</b>	<b>Sample size reported at first time point</b>	<b>Frequency of fatigue at first time point</b>	<b>Frequency of fatigue at last time point</b>
Schepers 2006	A, 6m, 12m	167	52%	70%
Van der Port 2007	6m, 12 m, 36m	223	68%	58%
Skaner 2007	3m, 12m	106	69%	58%
Sisson 1995	1m, 6m	13	92%	85%
Christensen 2008	10d, 3m, 12m, 24 m	138	59%	40%
Snaphaan 2011	2m, 18 m	108	35%	33%
Hellawell 1999 (subarachnoid haemorrhage people)	6m, 12m, 24m	28	65%	68%
Ogden 1994	10w, 12m	89	89%	86%
Noble 2008	24-251d, 335-672 d	73	59%	36%
Van Eijsden 2012	D, 24w	242	58%	55%
Radman 2012	6m, 12m	109	33%	34%

Abbreviations: A=admission; d=days; D=discharge; m= months; w=weeks

## Box 1

### Search strategies

#### Depression search strategy

Medline searched till 19/06/2013 (from date based on last published systematic review)

Stroke AND Depression (2004- )

- depressive disorder/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or depression/ or exp antidepressive agents/
- (depress\$ or dysthymi\$ or dysphor\$ or antidepress\$ or anti-depress\$).tw

#### Anxiety search strategy

Medline (2011- )

- anxiety/
- exp anxiety disorder/
- exp anxiolytic agent/
- (anxiety or anxieties or anxious or agoraphobi\$ or phobi\$ or panic disorder\$ or panic attack\$ or (obsess\$ adj3 compuls\$) or post?traumatic stress\$ or PTSD).tw.
- (feel\$ adj5 (apprehens\$ or dread or disaster\$ or fear\$ or worry or worried or terror)).tw.
- anxiety inventory.mp.
- anxiety scale.mp.

#### Emotional lability search strategy

Medline (2008- )

- crying/ or laughter/
- affective symptoms/ or emotions/
- (laugh\$ or cry\$ or weep or weeping or emotional\$ or pseudobulbar affect).tw.

#### Fatigue

Medline July 2013 all indexed articles, no start date

Fatigue AND stroke (to complement more extensive searches performed for published systematic reviews in 2012-See Duncan et al 2012)

#### Apathy, mania, psychosis, personality changes

Medline search on 15 JULY 2013; all indexed articles, no start date;

Filters: Humans, English language

Stroke AND

(apathy OR apathetic).af

(mania OR manic OR bipolar OR).af

(psychosis OR psychotic OR delusions OR hallucinations).af

AND personality.af

AND (irritability or irritable).af

AND (disinhibit\* or impulsiv\*).af

In September 2013, an additional search was done for euphoria.

stroke AND (euphoria OR euphoric OR hypomania).af

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