Fatigue after stroke
Neglected but important

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Declarations of interest

- **Funding** (Stroke Association, CHSS, Chief Scientist Office, Greater Glasgow and Clyde, Edinburgh Leisure, Scottish Government)

- **Royalties** - from Later Life Training (www.laterlifetraining.co.uk) that provide an Exercise after stroke course for exercise professionals, and from Elsevier for a book on exercise after stroke

- **Honoraria** for lectures on this topic
Questions

• What is fatigue after stroke (and how should we identify and ‘measure’ it)?
• How common is fatigue after stroke?
• Does it matter to patients?
• What causes fatigue after stroke?
• How should we treat fatigue after stroke?
• How can we implement exercise after stroke (and why might it be relevant)?
What is fatigue?

• Multiple definitions exist
• Normal fatigue: a state of general tiredness that is a result of overexertion and can be ameliorated by rest (De Groot 2003)
Abnormal (or pathological) fatigue

- Abnormal (or pathological) fatigue: weariness unrelated to previous exertion levels and usually not ameliorated by rest (De Groot 2003)

- Validity of other classifications of post-stroke fatigue is uncertain
  - central/peripheral?
  - mental/physical?
  - Primary/secondary?
How should we identify and measure it?

• Case definition for fatigue after stroke
  – Structured interview to identify clinically significant fatigue
  – Depression does not have to be excluded
  – Satisfactory reliability
  – ~ 40% of stroke patients have fatigue (Lynch J Psychosom Res 2007)

• Assessing fatigue severity
  – Systematic review of fatigue scales: 52 fatigue scales
  – We selected the four with the best face validity and tested for feasibility, validity and reliability
  – Fatigue Assessment Scale was the ‘best buy’ (Mead Stroke 2007)
Association between case definition and the scales
How common is it?

Study

Frequency (%)
Fatigue probably persists for months, at least

- Systematic review of longitudinal cohort studies
- 7046 citations; 101 full texts retrieved
- Nine studies (n=959) included
- Fatigue was assessed at a variety of time points after stroke (from admission to 36 months).
- Frequency of fatigue ranged from 35%-92% at the first time point.
- Frequency of fatigue declined in seven studies (n = 764) and increased in two studies (n = 195)

Duncan et al, J Psychosomatic Res 2012
Studies where fatigue decreased over time

Percentage of participants fatigued

Time since stroke onset

- < 3 months
- 3 – 6 months
- 12 – 18 months
- 24 months
- 36 months
It really does matters to patients!

- One of the most disabling symptoms after stroke (de Groot 2003)
- Interferes with rehabilitation (Morley 2005)
- Possibly an independent predictor of case fatality (Glader 2002)
- Affects return to full-time work (Medin 2006, Anderson 2012)
The Stroke Association National needs survey (MRC General Practice Research Framework)

Northern Ireland
14 practices

Scotland
15 practices

Wales
4 practices

England
11 practices

McKevitt Stroke 2011
Fatigue

- Need unmet: 43%
- Need met to some extent: 36%
- Need met: 21%
James Lind Alliance Survey: Priorities for ‘Life after stroke’ research

• JLA brings together patients and health care professionals to define the research agenda
• Survey of stroke survivors, carers and stroke researchers in Scotland
• 226 unanswered research questions were identified
• Top 10 included ‘What is the best way to treat and prevent fatigue?’

Pollock et al Lancet 2012
What causes fatigue after stroke
What causes post-stroke fatigue: Is it simply a symptom of depression?

- Fatigue is one of the symptoms in the diagnostic criteria for depression
- Anecdotally, patients with fatigue do not always fulfil diagnostic criteria for depression
Psychological associations with fatigue

• Systematic review (Simiao Wu, in preparation)
• 40 papers included
• Quantitative data synthesis underway
  – Preliminary results suggest associations between fatigue and both depression and anxiety
Identifying ‘causal’ factors

• Identify associations e.g. is depression associated with depression?
• Does depression cause fatigue?
  – Temporality
  – Strength of association
  – Dose response
  – Plausibility
  – Alternative explanation
  – Experiment
  – Coherence
Predictors of SF-36 vitality in International Stroke Trial

- 1400 surviving UK participants sent SF-36 at a mean of 64 weeks after randomisation, 1006 responded
- Regression analyses to determine independent predictors of SF-36 vitality
- Higher SF-36 vitality (i.e. less fatigue) predicted by
  - Lower age
  - Male sex
  - Higher emotional role score
  - Higher mental health score
  - (note: no association with OCSP subtype)
- But….this model predicted <30% variance in fatigue

Mead et al for UK IST collaborators, PloS One 2011
SF-36 vitality and SF-36 mental health at follow-up in survivors of IST

Pearson correlation coefficient 0.20, p<0.001, n=1004
So, what other factors might contribute to fatigue after stroke?

- **Pre-stroke fatigue**: though nature of fatigue after stroke is different (Flinn and Stube 2010)

- **Psychological factors (other than depression)**
  - Locus of control directed towards ‘powerful others’ (Schepers, Arch Phys Med Rehab 2006)

- **Biological**
  - ‘Central’ cause of fatigue?
  - Inflammation (central/peripheral)\
  - Cortisol dysregulation?
  - White matter lesions?
  - Impaired physical fitness?
‘Central’ cause of fatigue

• Anecdotally, patients report that fatigue starts at the time of stroke onset
• Fatigue more common in minor stroke than TIA (Winward Stroke 2009)
• Early reports suggested association with brain stem lesions (not confirmed in later studies including our analyses of IST dataset)
Associations with cognition

• Cohort study of 99 stroke patients
• Assessed in acute phase, 6 and 12 months
• Fatigue Assessment Inventory correlated with attentional and executive impairment (and depression and anxiety)
• Direction of causality is uncertain
• A third factor might cause both cognitive impairment and fatigue
• Perhaps fatigue is due to disruption of attentional networks in the brain?

Radman et al, Kutlubaev and Mead Neurology 2012
Inflammation and fatigue after stroke: pilot study n=28
Inflammatory cytokines and fatigue

• Higher level of proinflammatory cytokine interleukin-1 in the acute phase of ischemic stroke predicted development of fatigue at 6 months

• lower levels of its antagonist interleukin-1ra and anti-inflammatory cytokine interleukin-9 predicted development of fatigue at 12 months

Ormstad J Neurol 2011
White matter lesions?

- In SLE: white matter lesions are associated with fatigue
- In stroke: one study found an association \((\text{Naess J Neurol Sci 2011})\) whilst another did not \((\text{Snaphaan European Journal of Neurology 2010})\)
- Systematic review of fatigue and neuroimaging studies: no clear association with site of stroke lesion or WML \((\text{Kutlubaev et al Acta Neurologica Scandinavica 2012})\)
Neuroimaging and fatigue

- Standardised CT rating scores to determine associations with
  - White matter lesions
  - Site of lesion
  - Atrophy

- 90 patients: no clear association of neuroimaging features and fatigue at 1 month (Kutlubaev, in press)
Cortisol

- After stroke: cortisol is released as a stress response
- In chronic fatigue syndrome: cortisol dysregulation (either too high or too low) is sometimes present
- Our pilot study relating salivary cortisol with fatigue found no clear evidence of an association, but larger studies are needed
- One study (n=99) in minor strokes found no association (Radman et al. 2012)
Physical fitness and fatigue

Avoidance of, or reduction in physical activity

Physical deconditioning after stroke

Physical activity leads to fatigue
Associations between fitness and fatigue

• Analysis of baseline data from a clinical trial
  – Lower SF-36 vitality was associated with reduced leg extensor power
  – No association with economy of walking (an index of aerobic fitness) (Lewis Arch Phys Med Rehab 2011)

• Systematic review: too few data to reach any conclusions (Duncan Int J Stroke 2012)
Lower limb extensor power and SF-36 vitality

![Graph showing the relationship between leg extensor power in the unaffected leg (w/kg) and SF-36 vitality score.](image-url)
Is fatigue related to being less fit and active after stroke?

- Longitudinal cohort study of 170 people after stroke
- Determine natural history of fatigue
- Determine relationship between fatigue, reduced activity and fitness
- Obtain new data on patterns of activity after stroke
## Physical activity patterns in fatigued and not fatigued groups

<table>
<thead>
<tr>
<th>Activity</th>
<th>Fatigued (n = 24)</th>
<th>Not fatigued (n = 60)</th>
<th>Mann-Whitney U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of steps taken per day (IQR)</td>
<td>2483 (3746)</td>
<td>3424 (4227)</td>
<td>p=0.047</td>
</tr>
<tr>
<td>Median hours per day spent sitting or lying down (IQR)</td>
<td>20.5 (3.8)</td>
<td>20.0 (3.5)</td>
<td>p= 0.235</td>
</tr>
<tr>
<td>Median hours per day spent stepping (IQR)</td>
<td>0.55 (.82)</td>
<td>0.78 (.89)</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>Median hours per day spent standing (IQR)</td>
<td>2.5 (3.3)</td>
<td>3.1 (3.1)</td>
<td>p= 0.26</td>
</tr>
</tbody>
</table>
Associations between fatigue and reduced physical activity

• 84 patients had both fatigue assessment scale (FAS) and ActivPal data at 1 month post-stroke.

• Higher FAS (indicating more fatigue) were associated with:
  – less time standing ($r = -0.316$, $p<0.01$),
  – less time stepping ($r = -0.378$, $p<0.01$),
  – a fewer number of steps taken per day ($r = -0.375$, $p<0.01$)
  – more time spent sitting and lying down ($r=0.342$, $p<0.01$).
## Possible confounders of association between activity and fatigue

<table>
<thead>
<tr>
<th></th>
<th>Spearman’s correlation with fatigue assessment scale scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.044 (p = 0.622)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.576 (p = 0.000)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.496 (p = 0.000)</td>
</tr>
<tr>
<td>Gender</td>
<td>Mann-Whitney U test</td>
</tr>
<tr>
<td></td>
<td>p = 0.201</td>
</tr>
</tbody>
</table>
# Multiple regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>( p = 0.002 )</td>
</tr>
<tr>
<td>Time spent stepping</td>
<td>( p = 0.023 )</td>
</tr>
<tr>
<td>Anxiety</td>
<td>( p = 0.219 )</td>
</tr>
</tbody>
</table>

\[ F(3, 73) = 13.053, \ p < 0.0001. \] \( \text{Adjusted } R \text{ square} = 0.322 \)
Qualitative studies of patients experiences

• In-depth interviews can provide rich information about disease aetiology and effective treatments

• Our qualitative work
  – Fatigue frequently starts at the time of the stroke
  – Exercise, rehabilitation and good sleep are reported to improve fatigue

Barbour and Mead, Stroke Research and Treatment 2011
Pre-stroke fatigue

Perpetuating factors
- Physical inactivity
- Low mood, anxiety
- Poor sleep
- Locus of control

Trigger for fatigue
- Stroke lesion
- Disruption to attention networks
- Cortisol dysregulation
- Inflammation
- Physical inactivity

Perpetuating factors
- Physical inactivity
- Low mood
- Anxiety
- Poor sleep
- Locus of control
Cochrane review of interventions for fatigue after stroke

5097 citations scrutinised

29 full papers retrieved

6 RCT's excluded

3 RCT's included

21 non RCT's excluded

2 ongoing RCT's included

McGeough Cochrane library 2009
Completed trials of interventions for fatigue after stroke

• Fluoxetine for post-stroke emotional disturbance (n=83)
  – no effect on fatigue (Choi Kwan 2007)

• Tirilazad mesylate in women with subarachnoid haemorrhage (n=18)
  – Positive effect on fatigue in those that survived (Ogden 1998)

• Chronic Disease Self Management Programme in 1140 community-based subjects with several morbidities;
  – No effect on fatigue in the 125 (11%) with stroke (Lorig 2001)
Trials since publication of Cochrane review

• Modafinil in MS and after stroke
  – small study, modafinil well tolerated, improved fatigue in brainstem and diencephalic group but not in the cortical stroke group (Brioshi Eur Neurol 2009)

• Cognitive and Graded Activity Training (COGRAT)
  – Baseline period with no treatment
  – Then CBT plus treadmill training vs CBT alone
  – CBT plus treadmill training more effective than CBT alone (Stroke 2012)
COGRAT trial

- 8 rehabilitation centres in Holland
- 3 month ‘qualification period’
- Randomised 83 patients with severe fatigue on CIS scale (mean 3.9 yrs post-stroke)
- 12 weeks cognitive therapy (2 hr sessions per week for 12 weeks) or cognitive therapy AND graded exercise on treadmill) (2 hours twice a week for 12 weeks)
- Follow-up at end of treatment and 6/12
Checklist Individual Strength–subscale Fatigue (CIS-f) scores at the 4 time points for the cognitive therapy (CO) and CO with graded activity training (COGRAT) groups (n=83).
What can we learn from COGRAT?

• CBT is promising
  – Can we develop a brief intervention that can be afforded by the NHS and that is effective?

• Exercise is a promising intervention to treat post-stroke fatigue
  – How much, what sort and for how long is exercise needed to help reduce post-stroke fatigue?
Exercise after stroke

- Exercise improves physical function and fitness, and almost certainly reduces risk of recurrent stroke (irrespective of fatigue)
- Exercise training after stroke is recommended in RCP guidelines on stroke
- How should this be implemented?
Please enter your postcode into Eazq

Radius (miles)

SHOW A

Search

Please Note: Postcode must have a space in middle (e.g. AB12 3CD)

Centres within your specified radius: 31

Click on a numbered marker below to get directions to the chosen exercise centre from your location.
Referral pathways into community-based Exercise after Stroke

Health Care Professional role

Exercise Professional role

Stroke survivors discharged from hospital

Community-dwelling stroke survivors

Screening for absolute contraindications
Referral to EAS service
Complete referral form

Pre-exercise assessment

Exercise after stroke sessions in leisure centre

Continue exercise after stroke

Mainstream exercise services
Exercise professionals in the UK

- **Register of Exercise professionals** is an independent public register which recognises the qualifications and expertise of health-enhancing exercise instructors in the UK.

- **SkillsActive** sets down national occupational standards for exercise professionals
Exercise & Fitness Training After Stroke: Specialist Instructor Course
Management of fatigue

• Ask patients about fatigue on ward rounds and outpatient clinics
• Inform patients that fatigue IS a well-recognised phenomenon after stroke
• Screen for mood disorders and treat as appropriate
• Check for anaemia, diabetes, renal failure and other treatable medical conditions
• Leaflets from Stroke Charities
  – http://www.stroke.org.uk/factsheet/fatigue-after-stroke
SSRI for fatigue prevention?

• Fluoxetine 20mg daily, or placebo, for 6 months after stroke
  – FOCUS Trial (UK)
  – AFFINITY trial (Australia)
  – EFFECTS trial (Sweden)

• Primary outcome-modified Rankin score at 6 months

• SF-36 vitality is a secondary endpoint
Summary

- Fatigue affects ~40% of stroke survivors
- It matters to patients
- Potential causes
  - Depression, anxiety, psychological factors, cognitive impairment, reduced physical activity and biological factors
- Management
  - Rule out reversible medical condition, treat depression, advise graded exercise, consider CBT
Thanks to the funders

100 Years of Caring
CHEST, HEART & STROKE
SCOTLAND

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Further reading

Fatigue after stroke (Kutlubaev and Mead)

Exercise and fitness training after stroke: a handbook for evidence based practice. Eds Mead and van Wijck, Publisher Elsevier