



Olle Höök lecture 2009

Interpreting the evidence for rehabilitation following acquired brain injury

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Foundation for Rehabilitation Information
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Swedish Society for Rehabilitation Medicine



Objectives

- Approaches to grading of evidence
 - **Deriving recommendations**
 - **For evidence-based practice**
- Synthesis of evidence
 - **Using two different approaches:**
 - **Evidence from:**
 - Cochrane review of RCT evidence
 - Non-RCT evidence – new typology
- Future directions



Clinical guidelines / standards

- Increasingly relied on
 - **To guide clinical practice**
 - Individual treatment decisions
- Significant implications
 - **For resources, outcomes etc**
- Recommendations require
 - **Carefully researched evidence-base**
 - Safe, effective clinical care



Grading of recommendations

- Traditionally relies on

- **Quality of research evidence**

- Number of high quality studies
 - That support effectiveness of intervention

- “High quality” evidence

- **Has been synonymous with design**

- Often regardless of other quality indicators
 - Eg size of study
 - Robustness of methodology



Traditional evidence grading

Level of evidence	Type of evidence	Grade of recommendation
I	Randomised controlled trials (RCTs) Meta-analyses of RCT data	A
II	Other experimental trials <ul style="list-style-type: none">• Controlled clinical trials• Quasi -experimental designs	B
III	Non-experimental studies <ul style="list-style-type: none">• Cohort designs, descriptive studies	C
IV	Expert opinion <ul style="list-style-type: none">• Committee reports, respected authorities	D

Grade determined by design - regardless of quality or suitability



Quality rating

- >30 lists of quality criteria

- **For rating quality of RCTs**

- Moher D, Jadad AR, Tugwell P.

- Int J Technol Assessment Health Care 1996;12:195-208

- Jadad

- **3 main criteria**

- Van Tulder

- **19 criteria**

- **11 revised criteria**



Quality rating – Jadad criteria 1996

(Jadad AR et al Controlled clinical trials 1996; 17: 1-2)

<p>1. Was the study described as randomised?</p> <p>If yes:</p> <p>Was the method of randomisation appropriate? (E.g. computer generation, table of random numbers etc) (Add one point if appropriate, deduct one point if inappropriate)</p>	<p>Yes / No</p> <p>Yes / No</p>
<p>2. Was the study double blind?</p> <p>If yes:</p> <p>Was the method of blinding appropriate? (E.g. identical placebo etc) (Add one point if appropriate, deduct one point if inappropriate)</p>	<p>Yes / No</p> <p>Yes / No</p>
<p>3. Was there a description of withdrawals and Intention to Treat analysis</p>	<p>Yes / No</p>
<p>Yes = 1 No = 0: Total score</p>	<p>/5</p>



Reason for failure of Jadad criteria

■ Blinding

➤ **Proper consent procedures**

➤ Explain treatment alternatives

- Rarely feasible to blind patient in rehabilitation
- At best trials single blind

■ Intention to treat analysis

➤ **Rarely possible**

➤ TBI often an itinerant and non-compliant population

➤ Defaulters from treatment permanently lost to follow-up

■ So 2/3 conditions unlikely to be met



Van Tulder method 1997

(Spine 1997; 22: 2323 – 2330)

■ Adds to Jadad criteria

➤ **19 criteria**

➤ 11 for internal validity

➤ High quality score ≥ 6 *and*

➤ 6 descriptive

➤ High quality score ≥ 3 *and*

➤ 2 statistical

➤ High quality score ≥ 1

➤ **Adapted to ‘Other designs’ (eg cohort studies)**

➤ (Steultjens et al 2004)

Revised 2003

Spine 2003; 28:1290-9

➤ **11 criteria**

Internal validity only



Van Tulder criteria (Spine 2003)

- Randomisation adequate
- Treatment allocation concealed
- Groups similar at baseline
- Blinding
 - **Patient, Care provider, and Assessors**
- Co-interventions avoided or equal
- Compliance acceptable in all groups
- Drop-out rate described and acceptable
- Timing of outcome assessment
 - **similar in all groups?**
- Intention-to-treat analysis

**High quality:
'Yes' to 6/11**



RCTs not always appropriate

- Rehabilitation - complex intervention
- Challenges for RCTs
 - **Small numbers**
 - **Marked heterogeneity**
 - Patient group, intervention, setting
 - Outcomes relevant at each stage of recovery
 - **Ethical considerations**
 - Mental capacity
 - Expanding body of evidence for effectiveness
 - **Timescale measured in months or years**
 - Hinders wait-list control designs
- Alternative approaches



Broader range of evidence

- Extended base of research
 - **Other designs**
 - Cohort analyses
 - Longitudinal series
 - Real life practice
 - **Person-centred evidence**
 - User experience
 - Qualitative / Mixed methods
- Different typologies required



UK National Service Frameworks

- Set national standards
 - **Focus for NHS effort and resources**
- NSF for Long Term Conditions
 - **Published 2005**
 - Person centred approach
 - Life-long care / integrated services
- Evidence-based 'quality requirements'
 - **New typology of evidence**
 - Focus on quality of research
 - Regardless of design
 - Appropriate for long term conditions



NSF typology

- Two main groups of evidence
 - **Expert evidence**
 - Opinion based on experience
 - E1: Users/carers
 - E2: Professionals or other stakeholders
 - **Research evidence**
 - Categorised on 3 dimensions
 - Design
 - Quality
 - Applicability
 - Direct – evidence from population of LTNC
 - Indirect – evidence from other conditions



Classification of design

	Primary Research-based Evidence
P1	Quantitative research (e.g. experimental, longitudinal, cross-sectional)
P2	Qualitative research delivering descriptive data (e.g. focus group, rich narrative, consensus methodologies)
P3	Mixed methods (qualitative and quantitative) (e.g. a survey using both standardised measurement tools and detailed interviews)
	Secondary Research-based Evidence
S1	Meta-analysis of existing studies
S2	Secondary analysis of existing data
	Review-based Evidence
R1	Systematic reviews of existing research
R2	Descriptive or summary reviews of existing research



Quality rating

Quality assessment item	Score*
Are research question/aims and design clearly stated?	
Is the research design appropriate? for stated aims and objectives of research	
Are the methods clearly described?	
Is the data adequate? to support the authors' conclusions / interpretations	
Are the results generalisable?	
Total Score	/10

* Each quality item rated: "Yes" = 2, "In part" = 1, "No" = 0



Grade of recommendation

■ Grade A

- **>1 study of high quality score ($\geq 7/10$) *and***
- **At least one of these “Direct” applicability**

■ Grade B

- **1 high quality study *or***
- **>1 study of medium quality (4-6/10) *and***
- **At least one of these “Direct” applicability**

■ Grade C

- **1 medium quality study *or***
- **Lower quality studies only (grade 2-3/10)**
- **Indirect studies only**



But...

- In all of these methods
 - **Grade of recommendation**
 - Directly linked to research evidence
 - **What about other considerations**
 - Balance of benefits / harms
 - Patient choice
 - Convenience etc



GRADE

(Grading of recommendations, assessment development and evaluation)

- Two grades of recommendation
 - **Strong**
 - **(Weak) recommendation**
- Based on:
 - **Quality of evidence**
 - Trial-based
 - But opportunity to down or upgrade
 - According to quality of other evidence
 - **Balance of benefits and risks**
 - At level of individual or society



Process of applying GRADE

- By group consensus
- Identify important outcomes, e.g.
 - **Effect on symptom reduction**
 - **Significant morbidity**
- Grade each outcome for importance
 - **Scale 0-10** (rated by each group member separately)
 - Critical outcomes: those with mean score ≥ 7
 - Outcomes with mean score 4-6 – important, not critical
- Review quality of evidence
 - **For each outcome**
 - RCTs start 'high' – downgrade for limitations
 - Observational studies start low – upgrade for strong findings if minimal confounders



Adjusting for study design

Quality of evidence	Study design	Lower if *	Higher if *
High	RCT	Study Quality: 1-Serious flaws 2-Very serious flaws Consistency: 1-Important inconsistency Directness: 1-Some uncertainty 2-Major uncertainty Reporting bias Sparse data	Association: 2-Extremely strong 2-Very strong (no plausible confounders, consistent and direct) 1-Strong (no plausible confounders, consistent and direct)
Moderate	Quasi-RCT		
Low	Observational study		
Very low	Any other evidence		

* 1 = move up or down one grade (for example from high to moderate)
 2 = move up or down two grades (for example from high to low)



Process of applying GRADE 2

- Overall quality of evidence
 - **Across critical outcomes**
 - High, moderate, low, very low

- Balance of benefits and harms
 - Consider benefits and risks to patient
 - Benefits and risks to society (including costs)

- Recommendation
 - **Strong or weak based on**
 - Risk of benefit / harm
 - Quality of evidence



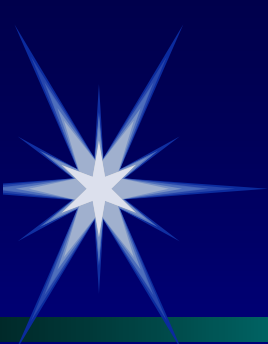
Advantage of GRADE

- Severe infection
 - **Early antibiotics vs no rush**
 - Not tested in RCTs
 - Never likely to be
- Guideline panels
 - **All likely to grade strong recommendation for early intervention**
 - Benefits outweigh the downsides
- GRADE allows for this



Disadvantages of GRADE

- Formalised consensus
 - **Still quite subjective**
- Benefits vs risks
 - **Consideration for patients**
 - Very different from society
- Eg rehabilitation
 - **Very few harms**
 - Patients like it
 - **But potentially very costly**
 - demonstrate benefits at level of cost savings



Application of research grading in the field of acquired brain injury

Cochrane Library – set up in the 1980s

- Archie Cochrane 1909-1988
- Resources will always be limited
 - **'Should be used to provide equitably the forms of healthcare which are shown to be effective by properly designed evaluation'**
- Randomised Controlled Trials
 - **More reliable information**
- Database of the RCT evidence
 - **Regularly reviewed and updated**
- Large international collaboration
 - **13 centres across the major countries**
 - **52 Cochrane review groups**
 - Diverse range of subjects





Cochrane Review

‘Multi-disciplinary rehabilitation
for acquired brain injury
in adults of working age’

Lynne Turner-Stokes

Ajoy Nair

Imad Sedki

Peter Disler

Derick Wade

Published: 2005 - Cochrane Injuries Group

Updated: April 2008



Review focus

- Adults of working age
 - **Fill gaps in literature**
 - Caseload of specialist neurorehab services in UK
- Inclusive approach
 - **ABI of all causes**
 - Trauma, stroke, anoxia, inflammation, tumour etc
 - **Trial design**
 - RCTs, Controlled clinical trials, Quasi RCTs,
 - MD Rehabilitation vs lower form of intervention
 - **19 Quality criteria - van Tulder**
 - **No meta-analysis - Synthesis of best evidence**



Specific questions

- Does organised MD rehabilitation
 - **Achieve better outcomes for this group of patients?**
- Does a greater intensity of rehabilitation
 - In terms of time or expertise
 - **Lead to greater gains?**
- Which type of programmes are effective
 - **And in which setting?**
- Which specific outcomes are influenced
 - **Dependency, social integration, mood, return to work etc**
- Are there demonstrable cost-benefits of MD rehab
 - **In terms of reducing long term care needs**



Search strategy and selection

	2005 Original	2008 Update	Total
Total titles	2300	1350	3650
Hand search of abstracts – 2 authors			
Short-listed for review	248	43	291
Selected articles	21	3	24
Supplementary reports / updates	6	1	7
Trials included	14	2	16



Best evidence synthesis

Category of evidence	Criteria
	<i>Consistent statistically significant findings in:</i>
Strong evidence	At least 2 high quality RCTs
Moderate evidence	At least 1 high quality RCT and At least 1 quasi-RCT or CCT
Limited evidence	At least 1 high quality RCT or At least 2 quasi-RCT or CCT
Indicative findings	At least 1 quasi-RCT or CCT
No evidence	Conflicting results between trials or insufficient data

Reference: Van Tulder MW et al 2003. Acupuncture for low back pain.



Synthesis

- 5 trials n=1258
 - **Mild TBI – ambulatory patients**
- Strong evidence
 - **Most pts make a good recovery**
 - No need for formal rehab
 - **Subgroup:**
 - Moderate – severe injury (PTA>1 hr)
 - Benefit from formal follow-up
 - May not present otherwise



More severe ABI – 10 trials

- 6 trials – three different models
 - **Out-patient rehab programmes**
 - 2 trials. n=182
 - **Co-ordinated community MD team**
 - 3 trials, n=265
 - **Specialist in-pt programme**
 - 2 trials, n=111
- 4 trials – different intensity of rehabilitation
 - **High vs low intensity programme**
 - 4 trials, n=351



Output: Out-patient programmes

- 'Moderate evidence'
 - **Out-pt therapy improves outcome**
 - Following stroke
- 'Limited evidence'
 - **More intensive OP programmes**
 - Associated with better outcomes
- 'Indicative evidence'
 - **Late intervention may be effective**
 - at least 1 year after stroke



Output: Community MD Team

- 'Limited evidence'
 - **Community MD Team improves outcome**
 - At the level of 'activity' (disability)
 - Especially when targeted towards specific goals
- Evidence of benefit for carers
 - **Has yet to be demonstrated**



Output: In-patient programmes

- 'Limited evidence'

- **In-pt rehab improves outcome for ABI**

- Functional activities

- Reduced carer distress

- Practical and ethical difficulties

- **Allocating pts with severe ABI**

- To no co-ordinated MD rehabilitation

- Some contamination of groups



Output: Intensive programmes

- 'Strong evidence'

- **More intensive programmes**

- Earlier function gain

- No evidence of a ceiling effect

- Is it cost-effective?

- **No formal cost-benefit analysis**

- **'Moderate evidence'**

- Leads to reduced length of stay



Discussion

- Studies highlight several problems
 - **Recruitment / retention of control groups**
 - **Differences between centres**
 - Additional heterogeneity
 - May outweigh benefits of increased numbers
 - **Lack of homogeneity in outcome measures**
 - Even where 'same measure' is used
 - Confound pooling to data for meta-analysis



Alternative methods

- NSF for Long Term Conditions 2002-5
 - **Broad based multi-source search**
 - Health and sociological literature
 - Evaluated using NSF typology
 - Each article assessed by at least 2 researchers
- Of 304 articles across whole NSF
 - **Rehabilitation for acquired brain injury**
 - 26 high/medium quality non-RCT studies
 - **Updated in April 2008**
 - 5 further studies



Additional synthesis

- 31 High/Medium quality trials
 - **Low quality trials excluded**
- Mainly cohort analyses
 - **Total >6600 patients**

- What more does this tell us?

Early and/or intensive rehabilitation

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RCT
N=351

Non-RCT
N=1905

NSF Typology

Strong evidence
Intensive rehabilitation
leads to
earlier functional gains
when fit to engage

**Strong evidence
(Grade A)**
Early rehabilitation
leads to
Reduced LOS in hospital
and
Improved outcomes

Specialist in-pt rehabilitation, for severe / very severe brain injury

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NSF Typology

RCT N=111	Non-RCT N=963
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Limited evidence

For
Improved outcome
(increased independence)
Reduced carer distress

Strong evidence (Grade A)

Require longer stay
significant function gains

Moderate evidence (Grade B)

Reduced needs for support
Long term cost savings

Specialist behavioural programmes

Cochrane

RCT N=0	Non-RCT N=140
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NSF Typology

Strong evidence (Grade A)

Improved social behaviour

**Moderate evidence
(Grade B)**

Reduced needs for support
Long term cost savings

Community based rehabilitation (TLU, day centre, out-patient, home-)

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RCT N=447	Non-RCT N=547
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Moderate evidence

For
Improved outcome

Limited evidence

More intensive OP
programmes are effective

NSF Typology

Strong evidence (Grade A)

Improved productivity
Reduced needs for supervision

Moderate evidence (Grade B)

Reduced institutionalisation

Late rehabilitation

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NSF Typology

RCT
N=49

Non-RCT
N=506

Indicative evidence
OP rehabilitation effective
at least 1 year after stroke

Strong evidence (Grade A)
Can still make function gains
5-10 years after injury

Specialist vocational rehabilitation / work support programmes

Cochrane

RCT N=0	Non-RCT N=433
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NSF Typology

Strong evidence (Grade A)
Increased rates of return to work
Cost-effective – overall gain to the tax payer



Long term outcomes

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RCT N=0	Non-RCT N=256
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NSF Typology

Strong evidence (Grade A)
Continue to make gains in independence
BUT
Employment rates fall 2-5 years after injury
Require long term support to maintain productivity



Putting these together
to formulate recommendations



Summary of recommendations

Intervention	Quality of evidence	Potential savings	Harms / risks	Recommendation
Early rehab	Mod	+	-	Recommend
Intensive	High	+	-	Strong
Specialist	Mod/high	++	-	Strong
Behavioural	Low/Mod	+	-	Recommend
Community	Mod	++	-	Recommend
Vocational	Mod/high	++	-	Strong
Late / ongoing	Low Mod	+/-	-	Conditional (selected cases)



Summary

- Substantial body of evidence
 - **MD rehabilitation for ABI is**
 - Effective
 - Cost effective
 - **Look beyond RCT-based evidence**
 - Cohort analyses
 - Longitudinal studies
 - Real life practice



The future

■ Practice-based evidence

- Horn, De Jong et al 2005 Arch Phys Med Rehabil 86 (12) suppl 2

➤ Large prospective multi-centre cohorts

- To answer the remaining questions
- Very large populations
- International data

➤ Future directions

- Agree manageable multinational dataset
- Open the black box of rehabilitation
- What works for which patients
- Fill gaps in current knowledge