Curative and palliative treatments for patients with disorder of consciousness

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Consciousness

NORMAL CONSCIOUSNESS

COMA

VEGETATIVE STATE

MINIMALLY CONSCIOUS STATE

Laureys, Owen and Schiff, Lancet Neurology, 2005
**Coma Recovery Scale-Revised**

Patients in VS and MCS: correct diagnosis

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**JFK COMA RECOVERY SCALE - REVISED**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date</th>
</tr>
</thead>
</table>

**AUDITORY FUNCTION SCALE**

- 4 - Consistent Movement to Command *
- 3 - Reproducible Movement to Command *
- 2 - Localization to Sound
- 1 - Auditory Startle
- 0 - None

**VISUAL FUNCTION SCALE**

- 5 - Object Recognition *
- 4 - Object Localization: Reaching *
- 3 - Visual Pursuit *
- 2 - Fixation *
- 1 - Visual Startle
- 0 - None

**MOTOR FUNCTION SCALE**

- 6 - Functional Object Use *
- 5 - Automatic Motor Response *
- 4 - Object Manipulation *
- 3 - Localization to Noxious Stimulation *
- 2 - Flexion Withdrawal
- 1 - Abnormal Posturing
- 0 - None/Flaccid

**OROMOTOR/VERBAL FUNCTION SCALE**

- 3 - Intelligible Verbalization *
- 2 - Vocalization/Oral Movement
- 1 - Oral Reflexive Movement
- 0 - None

**COMMUNICATION SCALE**

- 2 - Functional: Accurate
- 1 - Non-Functional: Intentional *
- 0 - None

**AROUSAL SCALE**

- 3 - Attention
- 2 - Eye Opening w/o Stimulation
- 1 - Eye Opening with Stimulation
- 0 - Unarousable

**TOTAL SCORE**

Denotes emergence from MCS *

Denotes MCS *
Treatment in DOC

1. Curative
   • Cognitive function
   • Physical function

2. Palliative
   Decrease side effects & improve comfort

   1. Pharmacological
   2. Deep brain stimulation
   3. Transcranial direct current stimulation (tDCS)

   4. Pain
   5. Spasticity
Curative treatments

Pharmacological
# Pharmacological treatment

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study (first author, year)</th>
<th>Number of patients and etiology</th>
<th>Diagnosis</th>
<th>Placebo control</th>
<th>Reported functional outcome</th>
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</thead>
<tbody>
<tr>
<td><strong>Dopaminergic agents</strong></td>
<td></td>
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<tr>
<td>Amantadine</td>
<td>Giacino (2012)</td>
<td>184 TBI</td>
<td>MCS/VS</td>
<td>Yes</td>
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<td>Schnakers (2003)</td>
<td>1 anoxic</td>
<td>MCS</td>
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<td>Patrick (2006)</td>
<td>10 TBI</td>
<td>Low responsive level</td>
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<td>Hughes (2005)</td>
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<tr>
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<td>Saniova (2004)</td>
<td>41 TBI</td>
<td>‘Persistent unconsciousness’</td>
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<td>Meythaler (2002)</td>
<td>35 TBI</td>
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<td>Levodopa</td>
<td>Matsuda (2003)</td>
<td>3 TBI</td>
<td>VS</td>
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<td><strong>Nonbenzodiazepine sedative</strong></td>
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<td>Zolpidem</td>
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<td>Lethargic</td>
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<td>Shames (2008)</td>
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<td>Singh (2008)</td>
<td>1 TBI</td>
<td>MCS</td>
<td>No</td>
<td>No effect</td>
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<tr>
<td></td>
<td>Brefel-Courbon (2007)</td>
<td>1 hypoxic</td>
<td>Akinetic mutism</td>
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<td>Positive</td>
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<tr>
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<td>Clauss (2006)</td>
<td>2 TBI, 1 anoxic</td>
<td>VS</td>
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<td>Clauss (2000)</td>
<td>1 TBI</td>
<td>Semi-comatose</td>
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<td><strong>GABA agonist</strong></td>
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<tr>
<td>Baclofen</td>
<td>Sara (2007)</td>
<td>1 non-TBI</td>
<td>VS</td>
<td>No</td>
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</table>

Amantadine

Dopaminergic agent (Parkinson)

Schnakers et al, *JNNP*, 2008
Zolpidem

Sedative-hypnotic agent (insomnia)
Indirect agonist of GABA$_A$ receptors
Curative treatments

Deep brain stimulation
Curative treatment: Deep brain stimulation?

Recovery of consciousness = recovery of thalamo-cortical (prefrontal) connectivity

Intralaminar nuclei stimulation induces “recovery” from minimally responsive state

Laureys et al, Lancet, 2000
Curative treatment: Deep brain stimulation?

Curative treatments

Transcranial direct current stimulation (tDCS)
# Why direct current?

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Population</th>
<th>Effects</th>
<th>Authors</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hemiplegic patients</td>
<td>Dexterity and strength</td>
<td>Hummel et al. Lancet, 2006</td>
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<td></td>
<td>Spastic patients</td>
<td>Spasticity &amp; ADL</td>
<td>Wu et al., Arch Phys Med Rehabil 2012</td>
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<td>Alzheimer’s patients</td>
<td>Memory</td>
<td>Ferrucci et al. Neurology, 2008</td>
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<td></td>
<td>Aphasic patients</td>
<td>Language</td>
<td>Baker et al. Stroke, 2010</td>
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</table>

Cheap & easy to use

Thibaut et al, Rev Neurol, 2013
Methods

- Direct current
- 2 mA; 20 minutes
- Anode: PFDL (F3)
- Randomised, double blind, sham controlled

Session 1
- CRS-R
- tDCS 20’

Session 2
- CRS-R
- tDCS 20’
- CRS-R
- tDCS 20’
Results

- 55 patients (43±18y; 25 VS/UWS, 30 MCS; 25 TBI; 35 chronic (>3 months)

- **15 responders**
  Patient who showed **signs of consciousness** after tDCS and not before tDCS or before and after sham
  - 2 VS; acute
  - 13 MCS (5>1y post insult)

Thibaut et al, submitted
tDCS – long term

**Effects last ± 90 minutes** (Hummel et al., Lancet 2006)
→ Short improvement, back to initial state

**Daily stimulations** (5days) (Antal et al., J Pain Symptom Manage 2010)
Improvement and extension of benefits
Randomised sham controlled double blind study

### Timeline

**Session 1**
- Day 1: CRS-R, tDCS
- Day 2: CRS-R, tDCS
- Day 3: CRS-R, tDCS
- Day 4: CRS-R, tDCS
- Day 5: CRS-R, tDCS
- 5 days

**Session 2**
- Day 1: CRS-R, tDCS
- Day 2: CRS-R, tDCS
- Day 3: CRS-R, tDCS
- Day 4: CRS-R, tDCS
- Day 5: CRS-R, tDCS
- 5 days

*CRS-R = 20 minutes

Prefrontal & precuneus stimulations

www.comascience.org
Palliative treatments

Pain in disorders of consciousness
Pain in brain death & VS/UWS

Noxious electrical stimulation

Low level disconnected cortical activation

Laureys et al, Neuroimage, 2002
Laureys, Nature Reviews Neuroscience, 2005
Pain in minimally conscious state

BUT...

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Sex</th>
<th>Age</th>
<th>ACC</th>
<th>AI</th>
<th>S2</th>
<th>S1</th>
<th>Thalamus</th>
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</tbody>
</table>

ACC = anterior cingulate cortex  
AI = anterior insula  
S1/S2 = primary and secondary somatosensory areas
Nociception and pain

Nociception Coma Scale - Revised

| Motor response | 3 - Localization to noxious stimulation |
|               | 2 - Flexion withdrawal                  |
|               | 1 - Abnormal posturing                  |
|               | 0 - None/flaccid                        |

| Verbal response | 3 - Verbalisation (intelligible) |
|                | 2 - Vocalisation                    |
|                | 1 - Groaning                        |
|                | 0 - None                            |

| Facial expression | 3 - Cry |
|                  | 2 - Grimace |
|                  | 1 - Oral reflexive movement/startle response |
|                  | 0 - None |

Score >3/9 = analgesic treatment

Chatelle et al, JNNP, 2012
Palliative treatments

Spasticity
Spasticity in DOC

Spasticity assessment (MAS*) in VS/UWS and MCS (n=57)

- **84%** showed spasticity
  **67%** had severe spasticity (MAS≥3)

- **Time since insult**: positively correlated with MAS scores

- **Pain** (*Nociception Coma Scale Revised*): positive correlation

* MAS=Modified Ashworth Scale

Thibaut et al, *in prep*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>5-20 mg 3 times daily</td>
<td>Increases the affinity of GABA for the GABAa receptor complex leading to an increase in presynaptic inhibition and reduction of synaptic reflexes</td>
<td>Sedation, weakness, hypotension, adverse gastrointestinal effects, memory trouble, confusion, depression and ataxia</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5-1.00 once daily</td>
<td>Same as above</td>
<td>Weakness, hypotension, ataxia, disco-ordination, sedation, depression and memory impairment. Prolonged use could increase the risk of addiction</td>
</tr>
<tr>
<td>Baclofen</td>
<td>5-20 mg 3-4 times daily</td>
<td>Centrally acting GABA analogue. Binds to GABAB receptor at the presynaptic terminal and thus inhibits the muscle stretch reflex</td>
<td>Daytime sedation, dizziness, weakness, fatigue, nausea; lowers seizure threshold Withdrawal seizures and hallucinations with abrupt discontinuation</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>4-36 mg daily</td>
<td>Imidazole derivative, with agonist action on alpha-2 adrenergic receptors in central nervous system</td>
<td>Dry mouth, sedation, dizziness, mild hypotension, weakness (less common than with baclofen) Liver enzymes should be monitored</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>25–100 mg 4 times daily</td>
<td>Interferes with the release of calcium from the sarcoplasmic reticulum of the muscle</td>
<td>Generalized muscle weakness, mild sedation, dizziness, nausea, diahhrhea, Hepatotoxicity</td>
</tr>
<tr>
<td>Phenol/alcohol</td>
<td>30 mg/kg</td>
<td>Chemical denervation of the muscles</td>
<td>Burning and dysesthesias. Damage of the sensory nerves with pain</td>
</tr>
<tr>
<td>Botox</td>
<td>10-15 units/kg</td>
<td>Inhibit the release of acetylcholine at the neuromuscular junction</td>
<td>minimal side effects. Rarely, children may become unusually floppy for a few days or weeks after high doses of Botox.</td>
</tr>
<tr>
<td>Intratecal baclofen</td>
<td>25–1000 mg daily</td>
<td>Binds to GABAb receptor at the presynaptic terminal and inhibits the muscle stretch reflex</td>
<td>Decreased ambulation speed and muscle weakness</td>
</tr>
</tbody>
</table>

Thibaut et al, *Brain Injury*, 2013
Physical therapy

- Stretching is very important to keep physiological amplitude of patient’s articulations
  - Every day on each articulation

- Massage could relax patient (but not sufficient)

- Be careful about irritative sources (bedsores, infections, etc)
  - ➔ pain, stress and fatigue increase spasticity

- Splints to hands and feet could be beneficial
**Soft splints**

**AIM:** Test the efficacy of soft braces on spastic upper limb to reduce spasticity in chronic VS/UWS & MCS

**Avantages:**
- Easy to apply
- Patient can be alone
- Soft and comfortable
- Several hours/day
Soft splints

**AIM:** Test the efficacy of soft braces on spastic upper limb to reduce spasticity in chronic VS/UWS & MCS

**Clinical benefits:**
- Spasticity decrease on fingers flexors
- Increase of hand opening
- Better improvement for patients without tendon retraction

![Graph showing MAS scores for Splints and Stretching](image-url)

Thibaut et al, *in prep*
Conclusions
Conclusions

• Current treatments: **Amantadine**, Zolpidem, (+ other drugs?)

• **Deep Brain Stimulation**

• **tDCS** could improve **cognitive** function in severe brain injured patients

• **Pain** ➔ Nociception Coma Scale-Revised

• Chronic patients ➔ improve their **comfort** and treat **spasticity**
Conclusions

- To treat spasticity
  - Botox: localized hypertonicity
  - Intrathecal baclofen pump: generalized hypertonicity
  - Baclofen, Diazepam, etc
  - Physical therapy: stretching & massage every day
  - Soft braces
  - !! Remove irritative causes
THANK YOU