Patients with disorders of consciousness: how to treat them?

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PhD Student
Coma Science Group

LUCA meeting
February 25th 2015
Pharmacological treatments

<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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic agents</strong></td>
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<tr>
<td>Amantadine</td>
<td>Giacino (2012)</td>
<td>184 TBI</td>
<td>MCS/VS</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Schnakers (2008)</td>
<td>1 anoxic</td>
<td>MCS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Patrick (2006)</td>
<td>10 TBI</td>
<td>Low responsive level</td>
<td>No</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Hughes (2005)</td>
<td>123 TBI</td>
<td>Coma</td>
<td>NA</td>
<td>No effect</td>
</tr>
<tr>
<td>Meythaler (2002)</td>
<td>35 TBI</td>
<td>MCS</td>
<td>Yes</td>
<td>Positive</td>
<td></td>
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<tr>
<td>Levodopa</td>
<td>Matsuda (2003)</td>
<td>3 TBI</td>
<td>VS</td>
<td>No</td>
<td>Positive</td>
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<tr>
<td><strong>Nonbenzodiazepine sedative</strong></td>
<td></td>
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<tr>
<td>Zolpidem</td>
<td>Cohen (2008)</td>
<td>1 anoxic</td>
<td>Lethargic</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Shames (2008)</td>
<td>1 anoxic</td>
<td>MCS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Singh (2008)</td>
<td>1 TBI</td>
<td>MCS</td>
<td>No</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Brefel-Courbon (2007)</td>
<td>1 hypoxic</td>
<td>Akinetic mutism</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Clauss (2006)</td>
<td>2 TBI, 1 anoxic</td>
<td>VS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Clauss (2000)</td>
<td>1 TBI</td>
<td>Semi-comatose</td>
<td>No</td>
<td>Positive</td>
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<tr>
<td><strong>GABA agonist</strong></td>
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<td></td>
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<tr>
<td>Baclofen</td>
<td>Sara (2007)</td>
<td>1 non-TBI</td>
<td>VS</td>
<td>No</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Adapted from Demertz et al, *Expert Rev Neurotheraputetics*, 2008
Amantadine

Dopaminergic agent (Parkinson)

Schnakers et al, JNNP, 2008
Zolpidem

Sedative-hypnotic agent (insomnia)

Indirect agonist of GABA$_A$ receptors

Chatelle & Thibaut, et al., 2014
Deep brain stimulation

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

Intralaminar nuclei stimulation induces “recovery” from minimally responsive state

Transcranial direct current stimulation

- Amantadine: risk of epileptic seizure
- Zolpidem: rare cases
- Deep brain stimulation: invasive surgery

→ new non-invasive and non-pharmacological technique

Transcranial direct current stimulation (tDCS)
Anode: ↑ excitability
Cathode: ↓ excitability
## Transcranial direct current stimulation

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Population</th>
<th>Effects</th>
<th>Authors</th>
</tr>
</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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<tr>
<td></td>
<td>Spastic patients</td>
<td>Spasticity &amp; ADL (activity of daily life)</td>
<td>Wu et al., Arch Phys Med Rehabil 2012</td>
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<tr>
<td></td>
<td>Alzheimer’s patients</td>
<td>Memory</td>
<td>Ferrucci et al. Neurology, 2008</td>
</tr>
<tr>
<td></td>
<td>Aphasic patients</td>
<td>Language</td>
<td>Baker et al. Stroke, 2010</td>
</tr>
</tbody>
</table>

➤ Cheap & easy to use

Thibaut et al, Rev Neurol, 2013
tDCS presumed mode of action

**Short term effects**  (Nitsche et al., J Physiol 2000)
Modification of neuronal excitability (action potential)

**Long term effects**  (Nitsche et al., Neuroscientist 2010)
Action on opening of ion channels (Na$^+$, Ca$^{2+}$)
Increase NMDA receptors excitability
→ improve neuronal excitability & plasticity?

Thibaut et al., Rev Neurol, 2013
Pilot study – single tDCS

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

Thibaut et al, Neurology, 2014
Results – single tDCS

- 55 patients (16f, 43±18y)
- 25 VS/UWS, 30 MCS
- 25 TBI, 30 NTBI
- 20 subacute, 35 chronic

Thibaut et al, Neurology, 2014

* p<0.001
15 responders
Sign of consciousness after tDCS and not before tDCS or before and after sham
• 2 UWS; acute
• 13 MCS (5>1y post insult)

3 MCS became EMCS
2 UWS became MCS

Thibaut et al, Neurology, 2014
Responders vs Non-responders: PET

Responders (n=8) vs non-responders (n=13)

Less hypometabolism
1. Stimulated area (left prefrontal cortex)
2. Long distance cortical area (precuneus)
3. Long distance sub-cortical area (thalamus)

Thibaut & Di Perri et al., submitted
Responders vs Non-responders: PET

Thibaut & Di Perri et al., submitted
Responders vs Non-responders: VBM

Responders (n=8) vs non-responders (n=13)

Less atrophy in:
1. Stimulated area (left prefrontal cortex)
2. Midline (mesiofrontal/ACC, PCC/precuneus)
3. Temporo-parietal cortex
4. Thalamus

Red: atrophy in responders
Blue: atrophy in non-responders
Pink: overlapping

Thibaut & Di Perri et al., submitted
Motor tDCS

89% of patients with DOC are spastic
Spasticity (MAS) correlates with NCS-R (Thibaut et al, in press)

→ How to decrease spasticity?

• Cathodal tDCS: C3/C4
• 1 mA – 20 minutes
• 2 sessions (real/sham)
• MAS and CRS-R before and after
• tDCS coupled with 8 electrodes EEG
• Record cortical activity before and after

In prep
Motor tDSCS

15 chronic patients (7 MCS, 40±15y, 8wo, 7 TBI)

**Results**

Group level: no ≠

Subject level: 1 patient

MASS

EEG: 1 responder: beta

Cathodal tDSCS decrease motor response?
Chronic patients with fixed joints?

In prep
Repeated tDCS

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

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

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**Diagram:**
- **session 1:**
  - tDCS, tDCS, tDCS, tDCS, tDCS
  - day 1, day 2, day 3, day 4, day 5
- **session 2:**
  - tDCS, tDCS, tDCS, tDCS, tDCS, tDCS
  - day 1, day 2, day 3, day 4, day 5, 1 week

* tDCS = 20 minutes

_In prep_
Repeated tDCS: results

Chronic MCS – N=24 (4 excluded)
(age: 47±16 years; time: 78±95 months; 12 TBI, 8 non-TBI)

* p≤0.05
Repeated tDCS: results

- 50% responders (10/20)
  - 5 patients responded after 1 tDCS
  - 5 patients responded after 2, 3 or 4 tDCS
Repeated tDCS in chronic patients at home or nursing home (multicentric study)

Protocol:
- tDCS over the prefrontal dorsolateral cortex, 2 mA, 20 min
- 5 days per week during 4 weeks (2 tDCS sessions – real & sham)
- Stimulations made by the family (video)
- Assessment: CRS-R before – after 4 weeks – two month later
- Double blind randomized study (2 months of washout)
- Chronic MCS patients (> 1y post insult) at home/nursing home
Thank you!