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What are the treatment options in patients with disorders of consciousness?

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Specificities of therapeutic interventions for DOC patients

- Absence of communication
- Lack of interaction with their environment
- Severe motor disability (e.g., spasticity)
- Constantly bedridden
- Fatigability
- Aphasia, blindness, deaf, etc.

⇒ No active rehabilitative interventions

« Hable con Ella »
Pedro Almodóvar
Pharmacological interventions
Pharmacological interventions

<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>
<td></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>
<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></td>
<td>Sanirova (2004)</td>
<td>41 TBI</td>
<td>‘Persistent unconsciousness’</td>
<td>NA</td>
<td>Positive</td>
</tr>
<tr>
<td>Meythaler (2002)</td>
<td>35 TBI</td>
<td></td>
<td>MCS</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Nonbenzodiazepine sedative</strong></td>
<td></td>
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<td></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>
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<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>
<td></td>
<td></td>
<td></td>
<td></td>
<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>

Amantadine

- Dopaminergic agent (Parkinson)
- Enteral administration, 6 weeks treatment (200mg/2*day)
- Side effects (seizure)


Schnakers et al, *J Neurol Neurosurg Psychiatry* 2008
Zolpidem

- GABAergic agent
- Enteral/oral administration (10mg)
- No side effects (sleep)

- 5% responders dramatic effects!

- 20% (12/60) improved behaviors after zolpidem but in only 1 patient changed of diagnosis (regained functional communication)

Figure 1 - Significant decrease of CRS-R total scores (ranging from 0 to 23) after zolpidem intake (interquartile range represented by errors bars) in the entire sample (n=60).

Thonnard & Gosseries et al, *Funct Neurol*, 2013
Zolpidem inhibits GPi

Chatelle et al, *Front Hum Neurosci*, 2014
Apomorphine

- Dopaminergic agent
- Subcutaneous administration (12h/day)
- Only case studies
- Side effects

Disability Rating Scale

Fridman et al, Brain Injury, 2009 & 2010
Pharmacological treatments

• Only a few pharmacological treatments

• Side effects / habituation

• Next:
  Apomorphine multimodal trial
  Zolpidem responders phenotype
Central Thalamic Deep Brain Stimulation
Projections from intralaminar nuclei


Striatum

Scannell et al. 1999
Consciousness ≈ thalamo-cortical

Intralaminar nuclei “reconnections” in spontaneous recovery from “vegetative” unresponsive state

Intralaminar nuclei stimulation induces “recovery” from minimally responsive state


MCS ➔ emerged – prolonged effects
• *sustained attention*
• *intelligible words*
• *functional objects use*
Deep Brain Stimulation conclusion

- DBS modulates specific cognitive and behavioral functions (arousal, functional limb movement, swallowing).

- Evidence of DBS carryover effects

- Limitations:
  - Strict inclusion criteria (e.g., no thalamic lesion)
  - Invasive
  - No randomized controlled study
Non-invasive brain stimulations

tDCS
Crossover RCT (n=55)

- No adverse events
- Clinical improvement in MCS only
- 13/30 responders (5 >1y post-insult)

Thibaut et al., Neurology, 2014
tDCS to unveil covert consciousness

- 67yo woman in UWS for 4 years after a subarachnoid hemorrhage
- Out of 7 standardized CRS-R she showed 1 localization to pain
- She demonstrated consistent response to command only after tDCS
- Neuroimaging exams were consistent with the diagnosis of MCS*

⇒ tDCS may facilitate motor execution of the command when cognitive functions are preserved

*Thibaut et al., Brain Stimulation, 2018
Neural correlates of responsiveness

8 tDCS responders versus 13 tDCS non-responders

Regional brain metabolism

Thibaut et al., Brain Stimulation 2015
Neural correlates of responsiveness

Brain connectivity – theta band

8 tDCS responders

14 tDCS non-responders

Thibaut et al., Brain Stimulation 2018
Double-blind crossover RCT (16 chronic minimally conscious pts) 5 sessions – 20 min prefrontal tDCS

Active session: significant time evolution (p<0.001)

Some patients responded after 1, 2 or 3 days of tDCS

9/16 responders (56%) & duration of the effects (1 week)

Single stim: 43% responders – effect size: 0.38 versus 0.57

Thibaut et al., Brain Injury 2017
5 sessions over M1 or DFPLC
7 VS and 3 MCS - chronic
→ All MCS showed clinical improvement immediately after treatment

5 sessions over DFPLC
7 VS and 6 MCS - chronic
→ Moderate clinical effects
→ Changes of EEG background in patients who improved clinically
Stimulating different brain regions

Group level: Prefrontal tDCS best area to target

Single-subject level: Patient’s tailored montage

Thibaut et al, 2014, 2017
Huang et al, 2017
Martens et al, submitted, Thibaut et al, submitted
Prefrontal tDCS better than targeting other areas?

Schiff, JAMA, 2010
Clinical translation

- Feasibility of tDCS for daily use
  - By relatives/caregivers (20 sessions)
- 27 MCS patients completed the study – compliance: $93 \pm 14\%$
  - No clinical effects
- 22 MCS patients received $\geq 80\%$ tDCS sessions
  - Significant effects & trend at 8-week follow-up – no AE

Martens et al, Brain Stim 2018
Conclusions

Pharmacological treatments

- Amantadine in TBI ➔ other etiologies?
- Zolpidem – 5% ➔ phenotype of responders
- Apomorphine ➔ randomized clinical trials

DBS

- Promising but invasive & no randomized clinical trials

NIBS

- tDCS is safe in severely brain-injured patients
- Prefrontal tDCS ➔ consistent clinical improvement
- Repeated tDCS ➔ increase duration of the effects ➔ increase number of responders
- Need patients’ tailored montage based on individual brain lesions
THANK YOU

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Additional slides
tDCS – diagnostic tool?

LIS, EMCS & MCS & 4 VS/UWS

Naro et al, Restor Neurol Neurosci 2015
Deep brain stimulation

transcranial Direct Current Stimulation

Amantadine

Zolpidem

Giacino, Fins, Laureys, Schiff, Nature Rev Neurol 2014
Repeated tDCS

16 patients in MCS (> 3 months; 12 TBI; 47 ± 16 y)

Treatment effect: delta CRS-R day 5 & day 12 (follow-up)

Effect size: 0.43

Effect size: 0.57

* p<0.05

Thibaut et al., Brain Injury, 2017
Targeting other areas?

Precuneus: critical hub for consciousness

Laureys et al, Lancet Neurology, 2004

Anode: posterior parietal cortex
Cathode: right SOR
2mA; 20min
5 tDCS sessions
Active and sham – 5d washout

Laureys et al, Lancet Neurology, 2004

Huang et al, Bain Stimulation, 2017
tDCS – Precuneus

Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: A sham-controlled randomized clinical trial

33 MCS >3 months post-insult (57±11y; 20 TBI)

9 responders (27%)
Sub-acute > chronic

No effect at 5day follow-up

Effect size : 0.31

Huang, ... Thibaut, Bain Stimulation, 2017
**Motor cortex**: common & efficient tDCS target

For patients with DOC?
- Immobilization, paresis…
- Improve behavioral responsiveness
- Covert consciousness

Martens et al., submitted
Motor cortex: common & efficient tDCS target

For patients with DOC?
→ Immobilization, paresis…
→ Improve behavioral responsiveness
→ Covert consciousness

Group level (n=10): no significant improvement (p=0.55; ES=0.10)

Single-subject level: 2 responders

Single stimulation & small sample size

Martens et al., submitted
Frontoparietal network
External awareness network
Critical for consciousness recovery

→ Stimulation of the external awareness network bilaterally

Hypometabolic areas
Preserved areas

Thibaut et al., J Rehab Med, 2011
46 patients with prolonged DOC. VS and MCS, TBI and non-TBI
4 anodes and 4 cathodes – 1mA; 20min
Single stimulation – active & sham
Behavioral & EEG assessments

• Group level: no improvement
  1 mA not enough?
  1 session not enough?

• 6 responders (13%) mostly TBI

• EEG in responders: increase in theta complexity after active
tDCS - no changes after sham tDCS

Martens et al., in prep
Vegetative state (n=116)

Minimally conscious state (n=84)

Traumatic

n=52

Non-traumatic

n=64

n=35

n=49

EMERGENCE
MCS
Dead
VS

Bruno et al, Coma and disorders of consciousness, Eds Schnakers and Laureys, 2012
tDCS

transcranial Direct Current Stimulation - tDCS

2 electrodes (or more)
Weak electrical current (1-2mA)

- Membrane polarization
  Anode: ↑ excitability
  Cathode: ↓ excitability

- Long term effects
  Neural excitability & plasticity (LTP-LTD)
  Ion channels (Na⁺, Ca²⁺)
  NMDA receptors

Nitsche et al., J Physiol 2000
Nitsche et al., Neuroscientist 2010
Neural correlates

- hypometabolic
- preserved

\( p < 0.05 \)

Thibaut et al., Brain Stimulation 2015
Neural correlates

fMRI 16 chronic MCS – 6 tDCS responders

Cavaliere et al. 2016 Frontiers Cell Neurosci
Fronto-parietal multichannels tDCS

Measure of complexity: LZW estimation per band and electrode

Percentage of change = (Post_LZW – Pre_LZW)/Pre_LZW*100 %

Delta

Alpha

LZW significantly decreases with tDCS under anodes, indicating that complexity decreases with tDCS in these bands

→ more structure in the data following tDCS?
tDCS & TMS

25 chronic DOC (12 VS/UWS; 10 MCS; 2 EMCS; 1 LIS)
Anode: OFC (Fpz) & cathode: Cz
TMS: MEP, RMT, ICI, ICF

Naro et al, Restor Neurol Neurosci 2015
What is consciousness?

Laureys, Trends in Cognitive Sciences, 2005
Why tDCS in DOC?

- No severe adverse effects
- Modulates spontaneous neuronal activity
- Inexpensive
- Reliable sham condition (for research)
- Easy to administer (clinical translation)
Neural correlates

Grey matter atrophy – VBM
- More atrophic in responders
- More atrophic in non-responders
- Overlapping

Brain metabolism – PET-scan
- hypometabolic
- preserved

Thibaut et al., Brain Stimulation 2015