Evidenztabellens S3-Leitlinie Neurologische Rehabilitation bei Koma und schwerer DoC im Erwachsenenalter

Die Evidenztabellen sind gegliedert nach Evidenztabellen für einzelne Studien und nachfolgend für Systematische Reviews/ Metaanalysen. Innerhalb dieser beiden Kategorien sind sie nach der Reihenfolge der Erwähnung im Leitlinientext sortiert. Die Referenznummer in der ersten Spalte bezieht sich jeweils auf die Kapitelnummern im Leitlinientext sowie die Nummerierung der Publikationen in den Kästen mit den Empfehlungen, die jeweils am Beginn der Kapitel stehen.
Die Bewertung in der Kategorie „Validity Rating“ bezieht sich für die einzelnen Studien auf die folgende Aufstellung nach Platz 2021.

Validity rating: yes (y), no (n), or not clear (nc)
Q1. Clear definition of eligibility criteria.
Q2. Clear definition and adequate assessment of study outcomes.
Q3. Reporting of side effects and acceptability.
Q4. Adequate follow-up assessment (long-term effects).
Q5. Clear definition and description of experimental and control condition.
Q6. Were participants randomly allocated (selection bias)?
Q7. Allocation concealment (selection bias).
Q8. Comparability of experimental and control groups at baseline (selection bias).
Q9. Blinded staff and patients during intervention and comparable treatment of randomized groups aside from investigated effects (performance bias).
Q10. Blinded outcome assessment (detection bias).
Q11. No selective reporting (reporting bias).
Q12. (Almost) Complete outcome data (attrition bias).
Q13. Intention-to-treat analysis reported.
Q14. Do the results sufficiently support the conclusions reported?

Evidence Tables for Single Studies

Evidence tables for single studies investigating **Rehabilitation programs** in people with DoC **(PICO-1)**

Table: 1 PICO: 1 Intervention: Rehabilitation program

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.2.1-(1)	**DeFina et al.,** 2010 Rest Neurol Neurosci retrospective within subject case series OCEBM Level of Evidence (LOE) (2011) **4**	ACP with 3 hours of therapy (PT, OT, ST) per working day in 3 sequential phases (2 weeks each) Phase 1: off-label drugs (e.g. Amantadine, Donezepil, Zolpidem) Phase 2: additional median nerve stimulation (MNS) 8 hours/day (every day) Phase 3: additional neutraceutical treatment (e.g. amino acids, omega 6 fatty acid, vitamins) Duration of ACP on average 12 weeks	Comparison within subject to own baseline and comparison to published cohorts (historic controls: 643 cases combined)	41 patients in UWS or MCS: UWS-TBI: 14 MCS-TBI: 7 UWS-nTBI: 18 MCS-nTBI:2 Time since injury (mean+/-SD): from 170+/-90 days to 216+/-107 days on average. Time since injury < 30 days: 0 Age (mean+/-SD): 27+/-10 in TBI and 47+/-18 or 53+/-10 in nTBI	Outcome measures: DRS, FIM, GCS, CRS-R Follow-up: 12 weeks (mean)	DRS, GCS, CRS-R, and FIM improved significantly at 12 w compared to baseline in all groups (*p* values not displayed due to several different group comparisons). Rate of emergence: UWS-TBI: 64% MCS-TBI: 100% UWS-nTBI: 56% MCS-nTBI: 100% All groups showed significantly more recovery than historic controls (*p* X^2 test from 0.02 to < 0.001 depending on type of comparison) Harm: not reported	total study: -- Q1: n Q2: y Q3: n Q4: y Q5: y Q6: n Q7: n Q8: n Q9: n Q10: n Q11: nc Q12: y Q13: y Q14: n	**0**	Sequential and comprehensive structured rehabilitation programme (ACP) leading to relatively high level of recovery compared to baseline / emergence from MCS compared to historic controls. Due a high risk of bias and hence a low quality of evidence our confidence in the estimates of therapeutic effect are limited. Accordingly, the data indicates a therapeutic option, but does not qualify a formal recommendation.

Table: 2 PICO: 1 Intervention: Rehabilitation program including transcranial extracorporeal shock wave therapy

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.2.1-(2)	**H. Lohse-Busch et al.** 2014 Case series OCEBM LOE (2011) **4**	2005 - 2012 All patients: -Different form of manual medicine -Physiotherapy -Medico mechanic devices -occupational therapy Additional: -TWEST (transcranial extracorporeal shock wave therapy) -4000 shock waves three times a week Period of 4 weeks	-	Inclusion: -Stable unresponsive wakefulness syndrome -period of 5 years Exclusion: -increase in any negative symptoms in the area of motor function or vigilance during treatment -Epileptic seizure -changes of medication -changes of domestic carers Five patients 4m 1f 1 HIE, 4 TBI Time since trauma 8-18 y Average age 38,6y (28-45)	Coma Remisson scale (KRS) Glasgow Coma Scale (GCS)	Increase in KRS of 135% after 4-8 treatment series	(e.g.) + Q1:- Q2:+ Q3:- Q4:- Q5:- Q6:- Q7:- Q8:- Q9:- Q10- Q11:- Q12:- Q13:- Q14:-	**0**	Patients profited from repeated rehab. Programs, including TWEST. Due to the study design w/o control condition, a specific treatment effect of TWEST could not be established, yet the study shows that a comprehensive rehab. Program can lead to improvements in the level of consciousness over time, even in a chronic DoC-population.

Table: 3 PICO: 1 Intervention: Rehabilitation program

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.2.1-(3)	**Sattin et al.** ; 2020 ; Arch Phys Med Rehab observational longitudinal, multicenter study (90 centers in Italy) OCEBM LOE (2011) **4**	Outcomes from the observational cohorts were examimed using propensity score (PS) methods, depending on whether they received rehabilitation. Patients were rated at baseline and 30 months later. Statistical adjusting for medication	Comparison within subject to own baseline. Comparison of patients who received rehabilitation with those receiving no rehabilitation.	364 patients: 188 w/o rehab. (controls) and 176 with rehabilitation Time since injury (median [IQR]): 1 [3] year in no rehab; 2.5 [3] years in rehab Etiology (no rehab/ rehab): TBI 31/56, Stroke 82/66, HIE 64/52, Other 11/2 Time since injury < 30 days: 0 Age (median [IQR]): 66 +/- 21 years in no rehab vs. 56 +/- 25 in rehab %MCS: 37% in No-Rehab; 49% in Rehab	Outcome measures: Diagnostic category of DoC, DRS Outcomes were identified by means of questionnaires by professionals Follow-up: 30 months (average) Type of rehab treatment: no Rehab, only PT, PT and cognitive therapy	DOC category / DRS: no difference at baseline between groups receiving rehabilitation and no rehabilitation 16% of MCS patients emerged at follow-up; 1% of UWS patients emerged 5% of UWS patients improved to MCS Rehab was associated with a significant decrease in disability levels by 6.5 DRS points ($p < 0.001$) and an improvement in disease severity. PT and PT/cognitive therapy were both associated with clinical improvement ($p < 0.001$). Harm: not reported	total study: -- Q1: n Q2: n Q3: n Q4: y Q5: n Q6: n Q7: n Q8: n Q9: n Q10: n Q11: nc Q12: y Q13: y Q14: n	**0**	Study uses comprehensive statistical methods to show that patients receiving rehab had a better outcome on average 30 mo.after baseline (more emergence from MCS, less disability). The statistical model tried to control for confounding factors between groups. Little information is given about the dose and type of rehab. and for the reasons that some patients did receive rehab while others did not. There is a very high risk of bias so that conclusions for clinical practice are very limited. With very low quality the study implies that rehabilitation treatment is associated with an improved outcome.

Evidence tables for single studies investigating **Drugs** in people with DoC **(PICO-2)**

Table: 4 PICO: 2 Intervention: Amantadine

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance forclinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.2-(1)	Giacino et al. 2012; NEJM OCEBM LOE (2011) **1** RCT	Amantadine for 4 weeks 2x100 mg/d: 14d 2x150 mg/d: 7d 2x200 mg/d 7 Increase of dose only, if change in DRS from baseline < 2. After 4 weeks dose reduction over 2-3 days.	Placebo for 4 weeks	UWS or MCS within 4-16 weeks after TBI with DRS > 11 n=184 after screening of 1170 patients Exclusion criteria for example pre-existing neurological condition, epileptic seizure within 4 weeks.	DRS after 4 weeks as primary endpoint 2 weeks of additional follow-up.	Amantadine group improved in DRS after 4 weeks compared to placebo (p=0.007) After follow-up, no difference between groups No difference in SAE	+ Q1: y Q2: y Q3: y Q4: y Q5: y Q6: y Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: n Q14: y	**2**	Amantadine leads to faster improvement of consciousness in traumatic DoC patients during active treatment. RCT with good and clear methodology and well-defined study population. Point of criticism: only 52% of patients who fulfilled inclusion criteria were enrolled as a potential risk of selection bias. Remains unclear, how long Amantadine should be given. Very high clinical relevance

Table: 5 PICO: 2 Intervention: Amantadine

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.2-(2)	Gao et al. 2020 OCEBM LOE (2011) **3** retrospective cohort study, not randomized	Treatment with amantadine after severe ICH in UWS patients Oral amantadine at a dose of 100mg twice daily. If there was no side effect, the dose of amantadine increased to 150 mg twice per day in the third week, and in the fourth week, the dose was further increased to a maximum dose of 200mg twice per day.	No control intervention Retrospective control cohort was matched on age, CRS-R-score, volume and location of hemorrhage.	Retrospective cohort study from 1/2015 to 7/2019 in Beijing Chaoyang hospital. 46 patients, 67.7% men. 12/46 patients were treated with amantadine.	Primary outcomes: time of consciousness recovery, Glasgow Outcome Scale scores after 5 months from onset.	Compared with the amantadine group, the consciousness recovery rate (50% vs 33.3%, P=.68) after 5 months in the control group was not significantly different. The awakening time for patients in the amantadine group was earlier than the control group (p=.03).	Total study - Q1: y Q2: y Q3: y Q4: y Q5: y Q6: n Q7: n Q8: n Q9: n Q10: n Q11: y Q12: n Q13: n Q14: y	**1**	As in TBI, Amantadine seems to accelerate DoC recovery, following severe ICH. Main limitations: Small retrospective study, no estimation for the effects of adjuvant therapies, duration of the medication varies, selection bias in agreement to participate (from the family's side). Results data partially difficult to interpret / understand.

Table: 6 PICO: 2 Intervention: Amantadine

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevanc e for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.2-(3)	Hughes et al. 2005 OCEBM LOE (2011) **3** retrospective cohort study, not randomized.	Patients received 100–200 mg of amantadine twice daily.	Individuals of similar injury severity, who did not receive the drug (not-exposed or controls).	123 TBI subjects. 75 (61%) males and 48 (39%) females, aged 17–87 years (mean=38±19 years). The majority sustained very severe brain injuries: 82% had a GCS≤5 and nearly all had multiple sites of brain injury on CT scan. Time since injury: unclear Inclusion-criteria: length of coma > 24hours, length of hospital stay > 14 days.	Emergence from coma, time until emergence from coma. No follow-up.	46.4% (13/28) of amantadine cases emerged from coma compared to 37.9% (36/95) of controls (n.s.). OR to emerge from coma with amantadine compared to no-amantadine 1.42 (96% CI 0.607-3.325, n.s.)	Total study: - Q1: y Q2: y Q3: y Q4: n Q5: y Q6: n Q7: n Q8: n Q9: n Q10: n Q11: y Q12: n Q13: n Q14: n	**0**	The study does not support the view that amantadine has an effect on recovery of consciousness However, they claim that the lack of treatment alternatives and anecdotal support for its use may warrant further study. The study design does not allow to draw conclusions for effect of amantadine

Table: 7 PICO: 2 Intervention: Amantadine & Cerebrolysin

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.3.5-(1)	Lee et al. 2020 OCEBM LOE (2011) **4** Retrospective case-control study	Amantadine (A) + Cerebrolysin (C) Amantadine to max. 2x200 mg per day Cerebrolysin to max. 2x2125 mg per day	Amantadine Amantadine to max. 2x200 mg per day, without Cerebrolysin	84 patients (42 per group) time since injury 3-165 weeks ∅ 25 w (9 pat. <4 weeks) group diff. for diseases time since injury, age CRS-R mean initial (A: 13.1±4.2 A+C: 8.2±3.1) <u>VS/MCS-/MCS+</u> A: 6/15/21 A+C: 15/24/3 p=0,001	CRS-R 48 h before first drug and 48 h before drug discontinuation	Change of CRS-R: A: 2.8±3.1 A+C: 4.2±3.3 p=0,027 <u>VS/MCS-/MCS+/EMCS</u> A: 3/8/25/6 A+C: 3/22/14/3 p=0,032 no sign. AE	Total study - Q1: n Q2: y Q3: n Q4: n Q5: n Q6: n Q7: n Q8: n Q9: n Q10: n Q11: nc Q12: y Q13: nc Q14: n	**0**	Authors claim that the dual strategy of Amantadine plus Cerebrolysin ist associated with better recovery in patients with prolonged DoC. The study carries a high risk of bias (selection, allocation; group differences, incomplete blinding) and lacks a control group w/o intervention. Both Amantadine with or without Cerebrolysin are associated with an increase in CRS-R. Overall this study has little relevance for clinical practice

Table: 8 PICO: 2 Intervention: Zolpidem

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.3-(1)	Whyte et al. 2009 OCEBM LOE (2011) **1** RCT, Cross-over design, double-blind	10mg Zolpidem (Z) given via feeding-tube immediately after baseline-CRS-R 2 days study (Z/P or P/Z) Replication protocol if first effect is positive	Placebo (P) given immediately after baseline-CRS-R	N=15 12 x UWS 3 x MCS Time since injury: ≥ 1 month 8 x TBI 5 x HIE 2 x others	CRS-R: Baseline and then every hour for 5 consecutive hours	1 patient (6.7 %) showed significant response and improved from UWS to MCS during the 5 hour observation phase. This positive response could be replicated in the replication protocol. 14 patients showed no change. There were no AE reported in Zolpidem-group	Total study + Q1: y Q2: y Q3: y Q4: nc Q5: y Q6: y Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: n Q14: y	**1**	The study used a rigorous design with little risk of bias so that the results can considered to be valid. Zolpidem was well tolerated but there was only 1 responder. This responder showed a very meaningful effect though. Since Zolpidem has a favourable risk profile, a single trial of Zolpidem may be warranted in DoC patients to identify responders.

Table: 9 PICO: 2 Intervention: Zolpidem

Ref. no.	Author, year, study type, evidenc e level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevanc for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.3-(2)	Whyte et al. 2014 OCEBM LOE (2011) **2** RCT with cross-over design (single dose)	Zolpidem, single dose 10mg on one assessment day.	Placebo on one assessment day.	84 DoC patients (traumatic and non-traumatic) Time since injury ≥ 4 months (range 5-87). Age range: 19-69. The Disability Rating Scale (DRS) was estimated through telephone interview with the caregiver for defining the patients´ baseline functional level.	Data collection occurred through a structured narrative reporting form developed for this project. The form was completed on each assessment day by the caregiver. In addition: The Coma Recovery Scale Revised (CRS-R).	4.8% of patients responded to zolpidem. Responders could not be distinguished in advance from non-responders. No demographic or clinical features were predictive of the response. Indicators of a drug response included increased movement, social interaction, command following, attempts to communicate, and functional object use. Responses typically lasted 1-2 hrs and sometimes ended with increased somnolence. Adverse events were more common on zolpidem than placebo, but most were rated as mild.	Total study + Q1: y Q2: y Q3: y Q4: n Q5: y Q6: y Q7: y Q8: n Q9: y Q10: n Q11: y Q12: y Q13: y Q14: y	**0**	10mg of zolpidem are associated with an improvement in consciousness in approx. 5% of chronic DoC patients This response typically occurs within an hour of drug administration but diminishes relatively quickly, leading to postdrug sedation in some patients. No simple clinical or demographic variables can clearly predict responder status. The study is well designed with low risk of bias. A Zolpidem trial may be undertaken in DoC patients.

Table: 10 PICO: 2 Intervention: Zolpidem

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.3-(3)	Thonnard et al. 2013 OCEBM LOE (2011) **2/3** Prospective, open-label trial followed by RCT if positive effect	<u>1) first study phase</u> Zolpidem 10 mg open label to all patients. For all patients, who improved consciousness category (UWS-> MCS or MCS -> eMCS) during Zolpidem trial, phase 2 was performed. <u>2) second study phase</u> RCT – placebo controlled, Cross-over-design with 10mg zolpidem or placebo.	In study phase 2 (RCT): placebo	N=60 patients m/f=42/18 time since injury: > 4 weeks (mean 4 years) UWS 28 MCS 32 TBI/nTBI 31/29	CRS-R ≥ 5x before zolpidem for eligibility and to define DoC category at time of baseline. CRS-R before and 1h after Zolpidem	Group level: no change Individual level: 12/60 (6.7%) patients improved on behaviour level and/or CRS-R level 1 patient improved enough to be enrolled in RCT part of the study. In this RCT phase, the initial improvement could not be replicated.	Total study: + Q1: y Q2: y Q3: n Q4: n Q5: y Q6: n.a. Q7: n Q8: n.a. Q9: n Q10: n Q11: y Q12: n Q13: y Q14: y	**0**	Very well-designed study with initial open-label screening phase and then RCT phase for presumed responders. Small or medium effects of Zolpidem on CRS-R and/or behaviour could only be found in 6.7% of patients and no patient changed DoC category due to Zolpidem in this very chronic cohort. Effects of Zolpidem on chronic DoC patients are infrequent and subtle. If subtle improvements are clinically meaningful may be an individual decision.

Table: 11 PICO: 2 Intervention: Zolpidem

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.3-(4)	Zhang et al. 2021 OCEBM LOE (2011) **4** Retrospective cohort study	Single trials of Zolpidem (Z) or Lorazepam (L) as part of a neurorehabilitation program.	None	146 patients, identified by chart review in a neurorehab hospital. 95 patients received either Z or L or both. Age: 36+/- 15 years Time since injury:median 62 days (IQR 22-246) UWS: 63 MCS: 74 eMCS: 9 TBI: 87 Stroke 11 HIE: 48	Positive trial was defined as more arousal and/or functional improvement as determined qualitatively in therapy sessions, 30 minutes after medication. CRS-R was collected regularly but not always on testing days. Responders were repeatedly exposed to the drug and re-tested in a small subset of patients (4)	Overall 11/95 patients (12%) were rated as responders. Z-Responders: 5/79 (6%) L-Responders: 6/43 (14%) 10.2% of TBI patients were responders to Z, 6.9% to L. No HIE patients responded to Z, 29% to L. Stroke patients responded to neither treatment. No AE/SAE reported.	Total study: - Q1: n Q2: n Q3: n Q4: n Q5: n Q6: n Q7: n Q8: n.a. Q9: n Q10: n Q11: n Q12: n Q13: n Q14: y	**0**	The study design is limited due to its retrospective nature, lack of a control condition and to the lack of standardized assessment of DoC. Yet, the study confirms positive rates of previous trials of Zolpidem and suggests, that TBI patients may benefit more than non-TBI patients. Lorazepam is suggested to be more effective in HIE than in TBI patients. Single trials of both drugs may be considered in DoC patients.

Table: 12 PICO: 2 Intervention: intrathecal Baclofen

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment (
2.3.4-(1)	Sarà et al. 2009 OCEBM LOE (2011) **4** Cases series	Intrathecal Baclofen (ITB) 100µg/d, dose increase over 30 days	n.a.	N=5 UWS with severe spasticity Etiology: SAH, ICH, TBI, HIE Time since injury 6-12 months	CRS-R, Disability Rating Scale (DRS), Modified Ashworth Scale (MAS) 6month FU period	Mean CRS-R increase of 8 points (min-max: 1-14points) at the end of 6 months Follow-Up. All patients improved, beginning 2 weeks after pump implantation. Improvement was clinically meaningful in most patients. Final Baclofen dose ranged from 200-399µg/d. Spasticity improved in all patients. AE/SAE not reported.	Total study -- Q1: y Q2: y Q3: n Q4: y Q5: y Q6: n Q7: n Q8: n Q9: n Q10: n Q11: n Q12: n Q13: n Q14: n	**0**	This is a small case series, yet it shows interesting effects of intrathecal baclofen, resulting in almost complete restoration of consciousness in 1 patient and meaningful improvements in the majority of patients. The mechanism of action remains unclear. The lack of a control condition is the major risk of bias. Intrathecal Baclofen should be considered a treatment option in DoC patients with concurring severe spasticity.

Table: 13 PICO: 2 Intervention: intrathecal Baclofen

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (+++ - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.3.4-(2)	Margetis et al. 2014 OCEBM LOE (2011) **3** Prospective, open label, observational study	Implanted intrathecal baclofen (ITB) pumps for the treatment of spasticity.	n.a.	8 DoC patients in UWS or MCS. TBI (n=6), HIE (n=1), acute obstructive hydrocephalus (n=1). Mean age 31.5 years (±8.1, range 20–47). Time since injury to ITB pump implantation 37.25 months (±33, range 5–108).	CRS-R, the Eastern Cooperative Oncology Group (ECOG) performance scale, and the Modified Ashworth spasticity scale (MAS). The mean follow-up period was 38 months.	Two of the patients showed a marked, persistent improvement that fulfilled the criteria of emergence from MCS. Two patients had their ITB pumps prematurely removed because of complications. The ECOG score was 4 for all patients and did not change during the study.	Total study: - Q1: y Q2: y Q3: y Q4: y Q5: y Q6: n Q7: n Q8: n Q9: n Q10: n Q11: y Q12: y Q13: n Q14: n	0	ITB might be associated with a significant improvement in the level of consciousness of two patients from a total of six that had a chronic ITB treatment. Limitations: The small number of patients ruled out any statistical analysis so only descriptive statistics are presented. No control or randomization. ITB may lead to an improvement in consciousness, where it is indicated for treatment of spasticity.

Evidence tables for single studies investigating **Positioning** in people with DoC **(PICO-3)**

Table: 14 PICO: 3 Intervention: Verticalization with robotic tilt table

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.4.1.-(2)	**Krewer, C. et al.** (2015) OCEBM LOE (2011) **2** RCT	Effect of a tilt table therapy with an integrated stepping device (Erigo®) on the level of consciousness. Interventions involved ten 1-hour sessions over a 3-week period.	Effect of a conventional tilt table therapy on the level of consciousness. Interventions involved ten 1-hour sessions over a 3-week period	50 participants in UWS or MCS Time since injury: 4 w. to 6 mo. after TBI, ICH or ischemic stroke. HIE patients only eligible in MCS Median GCS at randomization 9 (25-75% percentile 9-10) Age: 18 – 75 years	Coma recovery scale-revised (CRS-R) Modified Ashworth Scale (MAS) 3-week follow-up (FU)	CRS-R improved in both groups over time from median 12 points at baseline to 18 points after 6w. The Erigo® group improved by 3 points, the conventional group by 7 points (including FU). Improvement in the tilt table group was higher than in the Erigo® group (p=0.021 to end of intervention and p=0.005 to end of FU). Changes in spasticity did not differ between both groups.	Total study: ++ Q1: y Q2: y Q3: y Q4: y Q5: y Q6: y Q7: y Q8: y Q9: na Q10: y Q11: y Q12: y Q13: y Q14: y	**2**	Compared to the conventional tilt table, the tilt table with integrated stepping device *failed* to have any additional benefit for DoC patients. The study was not designed to analyze the effect of verticalization vs. non-verticalization, yet the clinical improvement of both groups suggests that **Verticalization** itself seems to be beneficial and should be administered to patients in DoC in early rehabilitation.

Table: 15 PICO: 3 Intervention: Verticalization with robotic tilt table

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.4.1-(3)	Taveggia et. al. 2015 OCEBM LOE (2011) **2** RCT	Verticalization with robotic tilt table (Erigo®) vs. verticalization with tilt table (Erigo®) plus hip/knee robotic passive movements (verticalization with a tilt table at 30°. After 10 min, patients were tilted head-upright at 65°. At 65°, a robotic system induced hip and knee flexion/extension movements. This cycle of flexion and extension of lower limb was repeated for 30 min at 18 steps/min. 3 sessions per week for 8 weeks (24 sessions)	Verticalization with a tilt table at 30°. After 10 min, the patients were tilted head-upright at 65° w/o robotic movements. 3 sessions per week for 8 weeks (24 sessions)	8 patients in UWS or MCS (4 DoC patients in intervention group and 4 patients in control group). Time since injury 3-18 months	CRS-R and LCF (Levels of Cognitive Functioning Scale) for DoC outcome; repeated blood pressure monitoring for evaluation of orthostatoc hypotension (OH) There was no follow-up.	For Consciousness: No change over time in CRS-R or LCF scores, no group differences For hemodynamic (OH) outcome: No syncopes occurred during study period. Verticalization including robotic leg movements (intervention group) significantly reduced time with OH compared to group without passive leg movements (control group).	Total study: + Q1: y Q2: y Q3: y Q4: n Q5: y Q6: y Q7: n Q8: y Q9: na Q10: n Q11: y Q12: y Q13: n Q14: y	**1**	In this chronic DoC population, 24 sessions with verticalization did not results in improved consciousness. The study did not include a control without verticalization. Verticalization with robotic passive leg movements leads to less time with orthostatic hypotension compared to verticalization without leg movements. In DoC patients prone to OH, verticalization with passive leg movements should be considered to avoid OH.

Evidence tables for single studies investigating **Multisensory Stimulation** in people with DoC **(PICO-4)**

Table: 16 PICO: 4 Intervention: Multisensory Stimulation

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures (Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.5.1-(1)	Di Stefano et al. 2012 ABCBA-Design OCEBM LOE (2011) **3**	3 sessions per week over 5 weeks according to the following phases of one week duration, each: A: Normal nursing B: Stimulation with biographically meaningful objects C: Meaningful objects together with meaningful narration	No control group; sequential design with A-B-C-B-A	N=12 patients in UWS (n=6) or MCS (n=6) with traumatic or non-traumatic brain injury. Age: 31 years (20-43). Time since injury: 5.5 months	Motor behaviours according to Wessex Head Injury Matrix (WHIM) during each stimulation phase	More complex stimulation lead to greater range of motor responses. Behaviors in phase C were more complex than in A and B ($p < 0.01$; ANOVA; F-value 15.3).	Total study: - Q1: y Q2: y Q3: n Q4: n Q5: y Q6: n Q7: nc Q8: nc Q9: nc Q10: nc Q11: nc Q12: y Q13: y Q14: y	1	Multisensory stimulation with biographically meaningful objects and verbal stimulation lead to more complex behavioural responses in a small cohort of young DoC patients. The validity is low due to low patient number and the non-randomized and non-controlled design. There is a concern about selection bias because the group is untypically young. It is unclear, whether the intervention has durable effects.

Table: 17 PICO: 4 Intervention: Multisensory Stimulation

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures (Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.5.1-(2)	Cheng et al. 2018 Withdrawal Design ABAB OCEBM LOE (2011) **3**	Phase B: Sensory stimulation program (SSP) with familiar auditory, visual, tactile, olfactory, gustatory stimuli. Order of stimuli presentation was randomized. 3 sessions per week with 20 minutes per session while wakeful state for 4 weeks per phase. Study duration: 4 months	Same patients during phase A without SSP during that phase	N=29 patients in UWS (n=11) or MCS (n=18) with traumatic (n=15) or non-traumatic (n=14) brain injury in one Chinese and one Italian rehab center Age: 48 +/- 19 years (20-79 years range). Time since injury: 1.37 months to 10.7 years (21 patients > 1 year)	Repeated CRS-R assessments during each study phase. Resting state fMRI in a subset of patients (n=7) at the end of each phase No follow-up	There was a significant ABAB phase effect (p=0.03; F(3) = 3.17; ANCOVA). CRS-R-scores were higher during B phases (treatment) in MCS patients (p=0.01) but not in UWS patients (p=0.27). fMRI showed higher activation during treatment phases in the right middle frontal gyrus, right superior temporal gyrus, and bilateral ventro-anterior thalamic nucleus. Time since injury and etiology did not interact with the positice main effect.	Total study: + Q1: y Q2: y Q3: n Q4: n Q5: y Q6: n Q7: n Q8: na Q9: n Q10: y Q11: nc Q12: y Q13: y Q14: y	1	A sensory stimulation program (SSP) with 60minutes of SSP per week leads to a small increase in CRS-R in MCS patients but not in UWS patients. The clinical significance of this CRS-R change remains unclear, no patient seems to have emerged from MCS. Given the limited study design without a separate control group, the validity of the study seems to be moderate. One weakness is that it remains unclear if there are durable effects. fMRI results corrobate the clinical effects in a subset of patients.

Evidence tables for single studies investigating **Auditory Stimulation and Music Therapy** in people with DoC **(PICO-4)**

Table: 18 PICO: 4 Intervention: Auditory Stimulation and Music Therapy

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.5.2-(1)	Castro et al., 2015 OCEBM LOE (2011) **3**	Excerpts of music (5 excerpts of favorite music, each 1 min) (and music-like noise in alternating order, counterbalanced between pts. and control subjects) The subjects own name (SON) and alternative first names pseudo-randomized (16 bits, 44100 Hz, 80 dB-A, 614 msec..Mean duration of sequence of first names: 1 min 26 sec.), presented after music/noise	music-like noise (20 Hz to 1 KHz 1 minute)	N= 13 3 female, 10 male Age: 41.5 +- 16 TBI: 7, Anoxia: 4, tumor: 1, metabolic: 1 Duration: 1.5 mths – 3 yrs (except 1: 20 days) UWS: 7, MCS: 6 13 age-matched healthy controls	<u>Before experiment:</u> CRS-R, EEG <u>After presentation:</u> <u>P300 and N200</u> <u>After 6 mths:</u> Supplementary behavioural responses	Controls: P300 and N200 higher in response to SON vs. neutral name (in both conditions) Pts: 7 pts. P300 and/or N200 discriminative response to SON More often in music than control condition (all of them favourable outcome; functional behavioural gains after 6 months, e.g. vis. Fixation or communication) All pts. (6/6) without discriminative response in both conditions no favourable change	Total study: + Q1: y Q2: y Q3: n Q4: n Q5: y Q6: y Q7: nc Q8: nc Q9: n Q10: nc Q11: nc Q12: y Q13: nc Q14: n	0	This is not truly a therapeutic intervention but more a diagnostic procedure as the music therapy was only a very short session. No assessment of functional outcome with standardized scale after intervention and at follow-up EEG-data interesting, but not sufficient to prove clinical intervention efficacy (also considering sample size) Recommendation: further studies needed to support efficacy of stimulation with preferred music and SOn

Table: 19 PICO: 4 Intervention: Auditory Stimulation and Music Therapy

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment (
2.5.2-(2)	O Kelly et al., 2013 OCEBM LOE (2011) **3**	Excerpts of preferred music (LM)/disliked music/ improvised music(white noise/silence/ (each 50-70 db), randomized Duration? Multiple baseline within-subjects design	n.a.	N= 21 9 female, 12 male Age: 22-76 TBI: 11, Anoxia: 9, ICH: 2 Duration: 2.2 mths – 14 mths UWS: 12, MCS: 9 (diagnosed with SMART and MATADOC) 20 age-matched healthy controls (13 female, 7 male, average age: 34 yrs)	EEG, HR, HRV, Respiration, behavioural responses (range of behaviors, e.g. following commands of auditory function scale of CRS-R, defined behaviors according to Wilson; video recordings)	Heterogenous results in patient groups, except: VS: eyeblinking significantly increased for LM; non-significant trend for eyes and mouth movement for LM Some VS pts. showed increases in EEG amplitudeand changes in physiological data in music therapy conditions	Total study: - Q1: y Q2: n Q3: n Q4: n Q5: n Q6: na Q7: na Q8: na Q9: y Q10: y Q11: n Q12: n Q13: na Q14: n	0	No cassessment of functional outcome with standardized scale after intervention, no follow-up EEG-data interesting, but not sufficient to prove clinical intervention efficacy (also considering sample size) High relevance to clinical practice Method. Weakness: lack of standardization of stimuli and assessments Recommendation: further studies needed to support efficacy of music therapy/auditory stimulation

Table: 20 PICO: 4 Intervention: Auditory Stimulation and Music Therapy

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.5.2-(3)	Pape TL et al. 2015 OCEBM LOE (2011) **2** RCT	Familiar Auditory Sensory Training (FAST): the patient is provided with customized recordings of stories told by people well known to the patient at least 1 year prior to injury. The stories represent specific events experienced by both the patient and the storyteller and were provided on compact discs, using portable players and noise cancelling headphones, while patients were awake (ie, eyes open). FAST protocols were conducted for 10 minutes 4 times per day, with at least 2 hours in between, for 6 weeks.	Placebo protocol is silence provided on compact discs, using portable players and noise cancelling headphones, while patients were awake (ie, eyes open). Placebo protocols were conducted for 10 minutes 4 times per day, with at least 2 hours in between, for 6 weeks.	15 participants in states of disordered consciousness (DOC), an average of 70 days (range: 29-170) after TBI. Intervention group: n=8 Placebo group: n=7	Disorders of Consciousness Scale (DOCS) Coma-Near-Coma (CNC) scale functional magnetic resonance imaging (fMRI)	Mean DOCS change was not different, but FAST patients had significantly (P = .049; 95% confidence interval [CI] = −1.51, −.005) more CNC gains. Mixed-effects models confirm CNC findings (P = .002). Treatment effect, based on CNC, is large (d = 1.88, 95% CI = 0.77, 3.00). Number needed to treat is 2. FAST patients had more fMRI activation in language regions and whole brain (P values <.05) resembling healthy controls' activation.	Total study: + Q1: y Q2: n Q3: n Q4: n Q5: y Q6: y Q7: y Q8: nc Q9:y Q10: y Q11: nc Q12: y Q13: n Q14: y	1	FAST resulted in improvement in CNC scale and increased neural responsivity to vocal stimuli in language regions 40 Minutes of FAST over 6 weeks had favorable clinical effects and effects on fMRI despite the small study population.

Evidence tables for single studies investigating **transcranial direct current stimulation (tDCS)** in people with DoC **(PICO-5)**

Table: 21 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: DLPFC

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.1.-(2)	Zhang Y. et al. (2020) Neurol Sci OCEBM LOE (2011) **4** Case-Series	20 anodal tDCS left dorsolateral prefrontal cortex sessions over 2 weeks = 10 consecutive working days) ERP oddball (subjects own name as deviant stimulus) paradigm FDG-PET Both, ERP and PET were performed 24-48 h before the tDCS	No control intervention	Xuab Wu Hospital 13 patients with DOC (8 UWS, 5 MCS), (months post injury 2.3 - 17.4) “vs” 6 “age-matched” healthy controls	Only real outcome measure: CRS-R pre-tDCS (14 days period) post-tDCS pre intervention: P300 CMRgl ratio analyses (voxel-based and ROI-vise)	CRS-R pre vs. post after 20 sessions of tDCS significantly improved in MCS (n=5) only (p=0.015) but not UWS (p=0.064). A correlation between CMRgl ratio in the right thalamus and right anterior cingulum and CRS-R was observed in MCS patients only. Higher CMRgl ratios in the right posterior cingulum (p=0.001), left (p=0.015) and right (p=0.022) superior frontal gyrus were observed in MCS vs UWS. P300 could only be identified in MCS patients and were comparable to healthy controls.	Total study: - Q1: y Q2: py Q3: n Q4: n Q5: na Q6: n Q7: na Q8: n Q9: na Q10: n Q11: n Q12: py Q13: na Q14: n	1	Overall the quality of the study design, data and population size is very poor. ERP and FDG-PET was performed before tDCS and not after! Therefore the question of a possible effect of tDCS on these parameters was not properly addressed. The assumption that residual brain activity in stimulated areas was necessary to achieve a behavioural response to tDCS is plausible but can not be confirmed by this study design because it could also have been the reason for a better spontaneous recovery of MCS patients.

Table: 22 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: DLPFC

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.6.1.-(3)	Zhang X. et al. (2020) Front Neurosci OCEBM LOE (2011) **3** Controlled cohort trial	A-B-design 2mA, 20 min, twice daily (5 days per week), 4 weeks: 40 sessions overall. 4 weeks sham tDCS (A) followed by 4 weeks anodal tDCS prefrontal (between Fp1, Fp2 and Fz, cathode over the neck) and left dorsolateral prefrontal (between F7 and Fz, cathode between Fz and F8) (B)	Sham stimulation within subject	Department of Rehabilitation, Wangjiing Hospital of China Academy of Chinese Medicine Sciences 10 Patients with post-traumatic psychomotor Inibition State (PIS), all TBI and MCS (duration 94-294 days after injury)	CRS-R and AES (apathy evaluation scale) EEG approximate entropy (ApEn) and cross approximate entropy (C-ApEn) Pre A, pre B, post B Painful stimulation of the affected and unaffected side	Pre A and Pre B values of CRS-R and AES were comparable (indicating no effect of sham), after B CRS-R and AES improved significantly ($p<0.01$). No En changes after A have been observed. ApEn under painful stimuli on the unaffected side was significantly higher after B in parietal and middle temporal EEG. C-ApEn was significantly higher under painful stimulation on the unaffected side between all regions of the unaffected hemisphere and affected hemisphere (except C-FP). Under painful stimulation of the affected side, C-ApEn was significantly higher between central and parietal regions of the affected hemisphere and central-frontal and central-midtemporal regions of the unaffected hemisphere.	Total study: - Q1: y Q2: py Q3: n Q4: n Q5: y Q6: na Q7: na Q8: na Q9: na Q10: n Q11: y Q12: py Q13: na Q14: py	1	CRS-R and AES improvement were consistent. Methods poorly explained. The interpretation of reported changes in entropy based EEG signal analysis in terms of information processing in terms of cortical connectivity is hypothetical. The anatomical interpretation of stimulus processing in affected and unaffected hemispheres is limited by very heterogenous lesion localization. Generally, the statistic results have to be interpreted with caution as many permutations of regions have been analyzed and results have not been corrected for multiple testing.

Table: 23 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: DLPFC

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.6.1.-(4)	Cavinato et al. Clin Neurophysiol. 2019 OCEBM LOE (2011) **2** RCT	Double-blind, sham-controlled, crossover design 2-weeks (10 sessions) active and 2-weeks (ten sessions) sham tDCS (2 mA, 20 min) over left DLPFC Washout between treatments > 2 weeks Anode (35cm2) was placed over the left dorsolateral prefrontal cortex (F3) and cathode to the deltoid muscle of the opposite side	Sham stimulation (Cross-over-design)	N=26 → 24 (12 UWS : (mean age 53 years (range ± 19 years), etiology: 5 anoxic, 2 posttraumatic, 2 different; duration p.o. mean 32 month (5 month – 11 years) 12 MCS (mean age 47 years (range ± 17 years), etiology: 3 anoxic, 7 traumatic, 2 different; duration p.o. mean 32 month (3 month – 7 years) (2 dropouts because pulmonar infection)	Resting state EEG (10 min) with EEG power spectra and coherence analysis directly before and after each stimulation session. JFK Coma Recovery Scale-Revised and the Western NeuroSensory Stimulation Profile (WNSSP) before each EEG session No follow-up	An increase of power and coherence of the frontal and parietal alpha and beta frequency bands and significant clinical improvements (significantly higher WNSSP total score ($t = 2.27$, $p = 0.04$). were seen after the active tDCS in MCS patients. UWS patients showed no significant changes in the power spectral analysis, higher frontal coherences in the delta frequencies ($t = 2.4$, $P = 0.03$). After the sessions of real tDCS no clinical changes were seen.	Total study: + Q1: y Q2: y Q3: n Q4: n Q5: y Q6: v Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: n Q14: y	0	Authors conclude that tDCS might modulate ongoing network dynamics through specific EEG frequencies, mainly in alpha and beta bands, likely due to changes in coupling of brain regions, in our context, anterior and posterior areas in patients with MCS. Development of specific tools, study of EEG coherence changes in the fronto-parietal network is needed to detect voluntary brain activity in patients with minimal behavioural output. The very large variability of the time post onset (3 month – 11 years) in both groups impedes a generalization of the results.

Table: 24 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: DLPFC

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.1.-(5)	Hermann et al. 2020 Sci Rep OCEBM LOE (2011) **4**	Single 20 min tDCS left dorsolateral prefrontal cortex (cathode right supraorbital cortex),	no control condition no control cohort	Paris, 66 patients, 60 included in analysis (24 UWS, 32 MCS, 4 exit-MCS)	CRS-R and high-density EEG at rest and during auditory oddball paradigm pre and post stimulation	3 patients clinically improved (1 UWS to MCS, 2 MCS to exit-MCS), 12 patients showed increased CRS-R scores after stimulation (20%, 4 UWS, 7 MCS, 1 exit-MCS, increase was significant (p=0.002, r=0.28), R = responders. Spectral power and connectivity in the theta-alpha-band: r+ showed sig. increase in theta power (max parietal) and alpha power. Response to tDCS correlated with an increase of functional connectivity (weighted symbolic mutual information) in the theta-alpha-Band. In the auditory oddball paradigm a larger and more sustanined P300 was observed in responders. Multivariate analysis indicated a significant stimulation by behavioral response interaction (p=0.045, F=4.2). Reported EEG-Effects (pre-post) correlated with tDCS electric field intensity in prefrontal cortices	Total study: + Q1:y Q2:y Q3:y Q4:n Q5:na Q6:n Q7:n Q8:na Q9:n Q10:n Q11:n Q12:py Q13:na Q14:py	1	The study was not designed to detect behavioral effects. Nevertheless, the reported EEG-analyses support the assumption that observed behavioral effects of prefrontal tDCS were correlated with a modulation of cortical connectivity and (conscious) cortical sensory information processing.

Table: 25 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: DLPFC

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.6.1.-(6)	Angelakis et al. Archives of Physical Medicine and Rehabilitation 2014, OCEBM LOE (2011) **3** Case series	Prospective, case series trial with follow-up at 12 months All patients received (same order) -sham tDCS for 20 minutes per day, 5 days per week, for 1 week - real @tDCS 1mA, for 20 minutes per day, 5 days - and real @tDCS 2mA, for 20 minutes per day, 5 days Anodal electrode (25cm2) was placed over the left primary sensorimotor cortex (C3) **or** the left dorsolateral prefrontal cortex (F3) (assigned alternately, but with exceptions, when patients had significant lesions or atrophy at the intended stimulation area) and cathodal stimulation (35cm2) over the right eyebrow (Fp2). One patient (MCS) with a second round (10 tDCS sessions) 3 months after initial participation.	Within subject Sham stimulation as the first stimulation	N=10 (3w/7m) 7 UWS, 3 MCS Age 19- 62 y, (mean 40, SD 13y), Time since injury 6 months to 10 years (mean 4,2; SD 3,7) Etiology: TBI (n=5), anoxia (n=4), and postoperative infarct (n=1).	Coma Recovery Scale-Revised assessed at 6 timepoints, including baseline, assessment at day 1, postsham assessment at day 5, post 1mA assessment at day 12, post 2mA assessment at day 19, and assessment at day 26 (1wk after completion of all stimulation in week 4).	All patients (n=3) in an **MCS** showed clinical improvement immediately after treatment (anodal stimulation: n=1 over F3, n=2 over C3; duration 6 month, 9 month, 4 years) . No patient showed improvement before stimulation. No patient in a PVS/UWS showed immediate improvement after stimulation, (1 patient showed improvement and change of status to MCS at 12-month follow-up; 1 patient (MCS) showed further improvement and emergence into consciousness at 12-month follow-up). The patient who received a second round of tDCS showed further improvement and emergence into consciousness after stimulation.	Total study: + Q1: n Q2: y Q3: y Q4: y Q5: y Q6: n Q7: y Q8: y Q9: n Q10: n Q11: y Q12: y Q13: n Q14: y	0	The authors conclude, that tDCS might be able support rehabilitation of patients in MCS – and patients with a short time post onset might profit more. They themselves relativize the outcome because of the small and inhomogeneous sample. However, the inconsistent stimulation sites further complicate a generalization of the results. Nevertheless, due to the lack of SAEs, a trial of treatment with tDCS seems possible.

Table: 26 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: DLPFC

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.6.1.-(7)	Carriére et al. Brain Sci. 2020 OCEBM LOE (2011) **3** RCT	Double-blind, sham-controlled, crossover design, Single session of one active and one sham tDCS (2 mA, 20 min) in a randomized order. Washout between sessions > 48h Anode (35cm2) was placed over the left dorsolateral prefrontal cortex (F3) and cathode over the right supraorbital region (Fp2).	Sham stimulation (Cross-over-design)	MCS or EMCS > 3 month p.o. N=11 (intention to treat n=13, 2 excluded because of missing behavioural data) (3f/8m) 6 MCS-, 4 MCS+, 1 EMCS Age 19- 62 y, (mean 46, SD 14y) Time since injury 3 – 25 months (median 5 month)	10 minutes of resting-state hdEEG pre and after tDCS/sham. Coma Recovery Scale-Revised No follow-up	Neurophysiological correlates: Group level (n=9) After correction for multiple comparison spectral power analysis showed no significant results. After corretction connectivity analysis didn´t show any significant change in any of the frequency bands. However, in uncorrected statistics, an increase in wSMI alpha connectivity was observed in the parietal region and an increase in wPLI alpha connectivity was observed in the fronto-parietal regions CRS-R: No treatment effect at group level (n=10, all MCS patients). Active stimulation: (Z = -1.39; p = 0.166) , Sham-stimulation (Z = -1.27; p = 0.203) Three patients improved after tDCS and showed new signs of consciousness, 6 patients showed a lower overall score in CRS after tDCS, but left no signs of consciousness. 5 patients showed a lower CRS-R total score after sham stimulation.	Total study: + Q1: y Q2: y Q3: n Q4: n Q5: y Q6: v Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: n Q14: nc	0	The authors conclude that neurophysiological changes can be observed after a single session of tDCS in patients with prolonged DOC, although they are not necessarily paralleled with significant behavioral improvements However, the inhomogeneous and small sample complicate a generalization of the results. Due to the heterogeneous behavioural and neurophysiological effects after active and sham stimulation, further studies with repeated tDCS sessions are needed.

Table: 27 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Motor Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures *(including ICF levels)* **Follow-up period**	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment *(*
2.6.2.-(1)	Martens et al. 2019, Brain Injury case series, randomized OCEBM LOE (2011) **3**	Single session of tDCS (2 mA for 20 min) and single session of sham tDCS. over M1. Active electrode placed over C3 **or** C4 (patients most affected side), cathode placed on contralateral supraorbital area. Cross-over design (washout > 24 h)	Sham tDCS	10 patients (49 ± 22 years, 7 ± 13 months since injury, 4 UWS, 6 MCS, 5 traumatic	CRS-R. (Total score, motor subscale score) for whole group and MCS group.	No overall significant treatment effect (Z = −0.62; p = .55; ES = 0.10). No treatment effect in the motor subscale (Z = 0.56; p = .75). For No significant treatment effect for MCS (Z = −0.26; p = .89; ES = 0.06). Single case level: 2 patients (1 UWS, 1 MCS) showed a new sign of consciousness after real tDCS	Total study: + Q1: nc Q2: y Q3: y Q4: n Q5: y Q6: y Q7: y Q8: y Q9: n Q10: n Q11: y Q12: y Q13: y Q14: y	0	M1 tDCS in patients with DOC is safe but failed at improving motor responsiveness at the group level. → the DLPFC seems to be currently the best candidate for enhancing signs of consciousness, especially patients in MCS. Important to further investigate M1 tDCS for DOC with more sessions, combination with motor training, or the concurrent stimulation of other areas.

Table: 28 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Motor Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results *)*	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.6.2.-(2)	Martens et al. 2020 NeuroImage Clinical RCT OCEBM LOE (2011) **2**	Single session active **multifocal** tDCS, 4 anodes, 4 cathodes, 1mA (per electrode), 20 min vs. Sham-Stimulation. Cross-over design. Washout min. 48 h Stimulation: Anodes: (bilateral frontoparietal areas): F3-F4 and CP5-CP6 Cathodes: (prefrontal and occipital areas) Fp2-Fpz and O1-Oz Washout between active -sham or sham-active 2-6 days	Single session sham-tDCs	46 patients in UWS (n=17), MCS (n=23), and EMCS (n=6) Time since injury < 28 days: Median 12 month (5-47) Age: Median 46 (35-59) Etiology: Traumatic (n=22), non-traumatic (n=24)	Primary outcome: CRS-R (group level), Secondary outcome:10 min of resting state electroencephalogram (EEG) (group level) directly before and after active or sham tDCS - Individual behavioural response patterns - relationships between baseline EEG metrics and behavioural outcomes	No tDCS behavioural treatment effect at group level (p = 0.222) Individual level: after active tDCS, 5 patients with new behaviours, but 3 patients lost behaviours consistent with conscious awareness. 37 patients did not show any behavioural changes (all UWS patients were in this group) Significantly increased EEG complexity in low frequency bands (1–8 Hz) following active tDCS	Total study: ++ Q1: y Q2: y Q3: y Q4: n Q5: y Q6: y Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: y Q14: y	0	The behavioural effect of multifocal frontoparietal tDCS varies across patients with DOC. Electrophysiological changes were observed in low frequency bands but not translated into behavioural changes at the group level. Due to the heterogeneous effects (gain and loss of previously demonstrated abilities) after active and sham stimulation, multifocal stimulation is currently not recommended or needs further studies with longer prospective protocols and customized montages. However, baseline theta EEG activity may contribute to building an individual response phenotype and to optimizing the therapeutic approach for DOC.

Table: 29 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Motor Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.6.2.-(3)	Thibaut et al. 2019 Ann Phys Rehabil Med RCT OCEBM LOE (2011) **2**	Single session of (tDCS) vs. Sham 1 mA 20 min. Cross-over design Two cathodes placed over the left and right M1 and 2 anodes over left and right prefrontal cortex.	Sham stimulation	14 patients after TBI, stroke or cardiac arrest 5 UWS, 9 (E)MCS 3 months post-insult >18 years (mean [SD] age 47 [19], range 25–73 years; 7 women)	Hypertonia of the upper limbs measured with Modified Ashworth Scale (MAS) and Coma Recovery Scale-Revised (CRS-R). Resting state electroencephalography	Group level: no treatment effect for the arm flexors (z = 1.500; P = 0.134; r = 0.28) Reduced spasticity in only finger flexors. (z = -2.344; P = 0.019; r = 0.44); No treatment effect in terms of CRS-R total scores (z = 1.223; P = 0.221; r = 0.23) or the motor subscale of the CRS-R (z = 0.169; P = 0.865; r = 0.03) At the group level, connectivity values in beta2 were higher with active versus sham stimulation. Relative power in the theta band and connectivity in the beta band were higher for responders than non-responders after the active stimulation.	Total study: ++ Q1: y Q2: y Q3: n Q4: n Q5: y Q6: y Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: y Q14: y	0	Potential benefit of tDCS for reducing upper-limb hypertonia in patients with chronic DOC → Large-sample clinical trials are needed to optimize and validate the technique.

Table: 30 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Motor Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Recommendation (2,1, 0,-1)	Conclusion / Comment
2.6.2.-(4)	Straudi et al. (2019) Brain Injury Case series OCEBM LOE (2011) **3**	10 sessions (five sessions/week for two weeks) of bilateral M1 anodal tDCS., (40 min, 2 mA).	Comparison within subject to own baseline	Ten chronic (> 12 month) patients in (MCS) following severe traumatic brain injury. (35.5 ± 12.6 years, 7 males and 3 females, 5.5 ± 5.4 years post trauma)	Coma Recovery Scale- Revised (CRS-R) administered two weeks before (T-1) and one day before (T0) the start of the experimental protocol, halfway through (after five sessions) (T1), at the end of the ten sessions (T2), after two weeks (T3) and after three months (T4). EEG assessment semi-structured diary for the patients' caregivers where they reported any new behaviour observed	Eight out of 10 patients showed new clinical signs of consciousness; a 2-point CRS-R improvement was detected in the last follow-up ($p = 0.004$). EEG upper α bandwidth was greater in the parietal site at T1 ($p < 0.034$). - significant correlation between behavioural and EEG indices at T1 ($r = 0.89$; $p = 0.001$).	Total study: + Q1: y Q2: y Q3: y Q4: y Q5: nc Q6: n Q7: n Q8: n Q9: n Q10: n Q11: y Q12: y Q13: y Q14: y	0	No control group. Unclear whether patients got additional behavioural therapy as they were inpatients to get a multidisciplinary rehabilitation program Bilateral stimulation over M1 may be a promising approach, because of the small sample size and the lack of a control group → results have to be confirmed in a greater RCT

Table: 31 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Parietal Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.3.-(1)	Guo et al.(2019); Front Neurosci OCEBM LOE (2011) **4**	HD-tDCS, 2 mA, anodal stimulation of precuneus (Pz vs. radially located surrounding cathodes over Cz, P3, P4 and POz)), 14 consecutive days, 2 sessions per day, 20 min each.	No control intervention Study: October 2016 – June 2017	Zhengzhou Central Hospital, 18 patients enrolled, N=11 completed study (5 VS, 6 MCS), mean age 52,8 years (30-71, no precuneus lesions), 9 Hemorrhage, 2 TBI, durations since injury 3-8 months.	CRS-R and 32-ch-EEG at T0, after first session (T1), 7 days (T2) and 14 days (T3), EEG coherence (spectral cross correlation and normalized power spectra)	9/11 patients (72%) showed increased CRS-R scores after 14 days (all 6 MCS, 3 VS), thereby VS remained unchanged whereas 4 of 6 MCS patients changed from MCS- to MCS+. EEG: coherence in Delta-Band between central and parietal regions, and between interhemispheric frontal and central regions decreased .	Total study: - Q1: y Q2: y Q3: y Q4: n Q5: na Q6: n Q7: na Q8: na Q9: na Q10: na Q11: y Q12: y Q13: na Q14: n	1	No control condition No control cohort No clear concept of delta coherence No long term follow up Very heterogenous etiology

Table: 32 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Parietal Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.3.-(2)	Huang et al. (2017) ; Brain Stimul RCT OCEBM LOE (2011) **2**	tDCS, 2 mA 20 min, 5 consecutive days, anodal stimulation of precuneus (Pz), cathode over right supraorbital	Active vs. sham in randomized order, 5 days washout	37 MCS patients, 33 completed study (mean age 57 +- 11 y, interval 6+-5, min 1 month after injury, months, 20 TBI, more than 1 month post injury, no medication.	CRS-R baseline, after day 5 and 10	Sign. Treatment effect after day 5 only (p=0.012, treatment effect 0.31) but not after 10 days, i.e. 5 days after last stimulation (p=0.135), 9 patients (27%) improved during active session, 2 patients (6%) improved during sham sessions (p=0.04 Fisher's exact test)	Total study: + Q1: y Q2: y Q3: y Q4: n Q5: y Q6: y Q7: y Q8: y Q9: y Q10: y Q11: y Q12: n Q13: na Q14: y	1	Good overall study quality and plausible effects after 5 days but no evidence for enduring effect. Direct comparison of the effect size showed stronger effects sizes of prefrontal stimulation (0.43 vs 0,31) and number of responders (56 vs 27%) (Martens et al. 2014).

Table: 33 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Parietal Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures *(including ICF levels)* Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.6.3.-(3)	Wang et al. (2020) ; Front Neurosci OCEBM LOE (2011) **4**	HD-tDCS (2mA, 20 min), precuneus, 14 consecutive days, 2 sessions in the afternoon.	No control intervention Study: January 2018 – August 2018	Zhengzhou Central Hospital, 14 enrolled, N=11 (2 VS, 9 MCS, 6 females, 5 males, mean age 54,2, 32-70 years, etiology: 2 TBI, 1 Stroke, 1 HIE, 10 ICH), duration since injury 8 – 320 days)	CRS-R and MMN (Mismatch negativity in frequency-deviant oddball paradigm) at baseline (T0), after first single session (T1), 7 days (T2) and 14 days (T3)	CRS-R sign. improved after 14 days in 11/11 pat., 1 VS -> to MCS-, 3 MCS- -> to MCS+; Analysis showed a significant effect of time (p=0.001, np2=0.665), sign. improvement of CRS-R compared to baseline after 7 days (p=0.016, Cohen's d=1.324) and 14 days (p=0.004, Cohen's d= 2.067), There was no sign. after T1; differences of T2 and T1, T3 and T1 and T3 and T2 were also sign. and showed a contin. increase of CRS-R. MMN analysis showed a sign. effect of time (p<0.001, np2=0.470) and deviation magnitude (p=0.001, np2=0.692), sign. improvements were shown after T1 (p=0.048, Cohen's d 2.857, T2 (p=0.004, Cohen's d 4.285) and T3 (p=0.011, Cohen's d= 3.943).	Total study: - Q1: y Q2: y Q3: y Q4: n Q5: na Q6: n Q7: na Q8: na Q9: na Q10: na Q11: na Q12: y Q13: na Q14: (y)	0	Very heterogeneous etiology and duration since injury, no control condition. Overall, it could not be ruled out that patients showed spontaneous recovery.

Table: 34 PICO: 5 Intervention: Transcranial Direct Current Stimulation (tDCS) / Target: Parietal Cortex

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures *(including ICF levels)* Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.6.3.(43)	Zhang Rui et al (2020) Front Hum Neurosci OCEBM LOE (2011) **4**	HD-tDCS (2mA, 20 min), precuneus, 14 consecutive days, 2 sessions /day (morning and afternoon)	No control intervention	Zhengzhou Central Hospital, n=35 (15 UWS, 51 +-9,6 y; 20 MCS, 52,3 +-16,9 y) (13 females, 22 males, 51,7 years mean, 30-320 days since injury, 7 TBI, 27 Hemorrhage)	CRS-R and EEG spectral connectivity at baseline (T0), after first single session (T1), 7 days (T2) and 14 days (T3) Follow up examination June 2019 (date of T0-T3 not reported) Network parameters: Average clustering coefficient, global efficiency, debiased weighted phase lag index (dwPLI)	MCS: 11 improved, 12 “recovered”; VS: 5 improved 4 “recovered”; CRS-R scores at T3 were sign. higher in MCS than VS, mean CRS-R scores improved from T0 to T3 in both groups the difference over time was not significant. Changes in Resting-State Network properties: Clustering coefficient showed no sign. Effect in UWS; in MCS average clustering coefficient and global efficiency sign. increased in beta and gamma band ($p<0.05$, FDR corrected), the global efficiency values decreased in delta band ($p<0.05$, FDR corrected) MCS patients showed a higher CRS-R increase at T3 compared to UWS ($p<0.05$, FDR corrected) Average Nodal Connection strength: UWS no sign. Changes, MCS mean delta dwPLI decreased in delta band (In Fig. 5 nicht nachvollziehbar), and increased in betaband over some electrodes (FC2, CP5, CP6, T8, P3, P7, P8, POz) and in gamma band over all electrodes except Fp1, F3, F4, O1, O2 and Oz.	Total study: - Q1: y Q2: y Q3: y Q4: py Q5: na Q6: na Q7: na Q8: na Q9: na Q10: na Q11: y Q12: y Q13: na Q14: py	1	Relatively large study sample, but very heterogeneous etiology and duration since injury, no control condition. Overall, it could not be ruled out that patients showed spontaneous recovery.

Evidence tables for single studies investigating **transcranial magnetic stimulation (TMS)** in people with DoC **(PICO-5)**

Table: 35 PICO: 5 Intervention: Transcranial Magnetic Stimulation (TMS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.4.-(1)	Xia et al. Front Neurol 8:182 (2017) Case series OCEBM Level of Evidence (2011) **4**	10 Hz rTMS to left DLPFC region for 20 sessions with 1000 pulses/session. In addition, routine rehabilitation	No controls. Pre-Post-Design	16 patients (5 MCS-; 11 UWS). Etiology: 2 TBI, 5 HIE, 8 ICH, 1 ischemic stroke. Time since injury 3-35 months (mean+/-StdDec: 8+/-8 months); age 43+/-12 years.	CRS-R at baseline and 4 additional time points, the last 10 days after final rTMS. Clinical Global Impression-Improvement (CGI-I) scale on day 30, performed by family member Safety/side effects	On the group level, CRS-R scores improved by average 1.3 +/- 1.5 points after 30 days compared to baseline (p=0.007). Consciousness diagnosis improved in 5 patients (from MCS- to MCS+ in 2 patients, from UWS to MCS- in 1 patients and from UWS to MCS+ in 2 patients). MCS patients improved significantly in CRS-R (p=0.04) while UWS patients on the group level did not (p=0.066). First positive treatment effects could be observed starting after 10 days of rTMS. Relatives rated global clinical improvement with good correlation to CRS-R improvement, No adverse events related to intervention.	Total study: - Q1: y Q2: y Q3: y Q4: n Q5: y Q6: n.a. Q7: n.a. Q8: n.a. Q9: n.a. Q10: y Q11: y Q12: y Q13: nc Q14: y	0	20 sessions of 10 Hz rTMS to left DLPFC in chronic DoC-patients with a stable CRS-R baseline leads to an improvement in CRS-R on the group level, which is carried by positive effects in the MCS subgroup of patients. Weaknesses are the lack of a control condition and the short follow-up. In conclusion, it is unclear, whether the positive effect of rTMS in MCS patients is attributable to rTMS or spontaneous recovery. Yet, it is noteworthy, that all MCS patients improved clinically while under rTMS treatment.

Table: 36 PICO: 5 Intervention: Transcranial Magnetic Stimulation (TMS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.6.4.-(2)	Ge et al. Exp Ther Med (2021) Retrospective Cohort Study OCEBM Level of Evidence (2011) **3**	10 Hz rTMS to right DLPFC region for 20 sessions with 1575 pulses on consecutive days. In addition, "standard rehabilitation"	Patients, who were eligible for rTMS treatment but where caregivers/legal surrogates declined rTMS intervention were chosen as controls and received no rTMS intervention.	15 UWS patients in the intervention rTMS group (age 61+/-2 years; 8 TBI, 7 ICH); CRS-R at baseline (3x) 3.7+/-0.7 17 UWS patients in control group (age 60+/-2 years; 8 TBI, 9 ICH); CRS-R at baseline (3x) 3.8 +/-0.8 It is somewhat unclear/confusing what the disease duration was; in the inclusion criteria it is suggested that it is at least 20 days.	CRS-R at baseline and after 20 days; no further follow-up. MEP latency and central motor conduction time (CMCT)	Clinical Outcome: CRS-R increased in rTMS group more than in Control group (change scores of 3 in rTMS vs. 1 in controls; $p<0.001$). In rTMS group, 87% of UWS patients recovered to MCS- while only 29% of control patients achieved this ($p=0.0016$). MEP Outcome: Significant decrease of MEP and CMCT only in rTMS group but not in control group. No adverse events / "specific side effects" were recorded	Total study: - Q1: n Q2: y Q3: y Q4: n Q5: n Q6: n Q7: n Q8: y Q9: n Q10: n Q11: n Q12: y Q13: n Q14: nc	0	20 sessions of 10 Hz rTMS to right DLPFC in "early" UWS patients was associated with more improvement on CRS-R after 3 weeks and led to more improvement in consciousness diagnosis. rTMS treatment was safe. Weaknesses are the retrospective design, lack of sham rTMS, insufficient detail on patient history, especially time since injury and the short follow-up. This study provides some evidence with very little confidence in the results based on study design/reporting that rTMS may lead to faster recovery of consciousness in UWS patients, early after brain injury.

Table: 37 PICO: 5 Intervention: Transcranial Magnetic Stimulation (TMS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.4.-(4)	Xie et al. Neural Regen Res (2012) Cohort study OCEBM Level of Evidence (2011) **3**	10 Hz rTMS to right DLPFC region for 20 sessions within 4 weeks. No details about further rehabilitation treatment provided	No controls. Pre-Post-Design	10 patients (2 comatose, 5 UWS, 3 MCS); etiology stroke in all cases (4 ICH, 6 ischemic); age mean 62 +/- 12 years; duration of disease 15-61 days (mean 49 +/- 14 days)	CRS-R and GCS at baseline and 6 additional time points, the last after 4 weeks after final rTMS. No further follow-up. Power in EEG bands	Clinical Outcome: Increase in CRS-R during intervention period. No details given. Maximum increase of CRS-R seemed to be 4 points. EEG Outcome: Increase in alpha Power, which correlated with increase in CRS-R and GCS with stable values after 2 weeks. No adverse events related to intervention.	Total study: -- Q1: y Q2: n Q3: y Q4: n Q5: n Q6: n.a. Q7: n.a. Q8: n.a. Q9: n.a. Q10: nc Q11: nc Q12: nc Q13: nc Q14: n	0	20 sessions of 10 Hz rTMS to right DLPFC in a stroke/DOC cohort in the early subacute phase were associated with increases in CRS-R. The increase in CRS-R correlated with increases in alpha Power in the EEG. Weaknesses are the lack of a control condition, the early clinical setting, the lack of detailed outcome information and the short follow-up. There is not enough data provided to draw any conclusions from this study apart from rTMS being well tolerated in all patients.

Table: 38 PICO: 5 Intervention: Transcranial Magnetic Stimulation (TMS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --)	Relevance for clinical practice (2,1,0, -1)	Conclusion / Comment
2.6.4.-(4)	He et al. 2020 Front Neurol. Cohort study OCEBM Level of Evidence (2011) **3**	20 sessions of rTMS over left DLPFC with 5 sessions per week for 4 weeks. Each session with 2000 pulses at 20 Hz at intensity 100% resting motor threshold.	No controls. Pre-Post-Design Responder analysis	25 patients in UWS (9 TBI, 10 stroke, 6 HIE) for at least 3 months (mean: 5+/-1.5 months and 5.2 +/- 2.4 months). Age 52+/- 11.7 years and 46 +/- 11.6 years for responders and non-responders. CRS-R at baseline 5.2 +/- 1.6 and 5.0 +/- 1.4 for responders/ non-responders.	CRS-R at baseline and at the end of 4 weeks treatment. Quantitative EEG (19 channels) with analysis of power in different frequency bands. No further follow-up beyond end of intervention.	<u>Clinical outcome:</u> 10/25 (40%) patients had improved consciousness at end of study with CRS-R 12.6 +/- 2.0. 15/25 patients had no improved consciousness with CRS-R 5.5 +/- 1.4. No HIE patient was among responders. <u>EEG-Analysis:</u> Responders had higher alpha power before rTMS than non-responders (p=0.03). Responders displayed decreased frontal delta power as a rTMS effect (p=0.04).	Total stuy: - Q1: y Q2: y Q3: n Q4: n Q5: y Q6: n.a. Q7: n.a. Q8: n.a. Q9: n.a. Q10:n.a. Q11: nc Q12: n Q13: nc Q14: y	0	40% of UWS patients experienced a significant improvement in CRS-R after 4 weeks of rTMS at 20 HZ to left DLPFC. Responders are characterized by higher alpha power in EEG. No HIE patient had a clinical benefit. Main weaknesses are the lack of a control group and limited data on clinical improvement of patients as well on any rehab efforts. It is unclear, whether the longitudinal effects are attributable to rTMS or to spontaneous recovery. In conclusion, high rate of recovery under rTMS may show a signal in favor of this treatment.

Table: 39 PICO: 5 Intervention: Transcranial Magnetic Stimulation (TMS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.4.-(5)	Legostaeva et al. 2019; Brain sci 9(5) Cohort study OCEBM Level of Evidence (2011) **3**	10 sessions of rTMS to left angular gyrus at 20 Hz with 3200 pulses per session over period of 2 weeks. In addition, 10 sessions of PT (45-55min) as well as robotic verticalization.	No controls. Pre-Post-Design	39 patients (16 UWS, 22 MCS); age median 36 +/- 20 years in UWs and 36 +/- 19 years in MCS; etiology HIE 26 (15 in UWS and 11 in MCS group), TBI in 12 (1 in UWS and 11 in TBI group). Disease duration 21 (3-39 range) months in UWS and 20 (3-38) months in MCS group. CRS-R at baseline 5 (4-7 range) in UWS and 14 (7-21) in MCS group.	CRS-R at baseline and 2 days after last rTMS (= 2 weeks + 2 days). No further follow-up.	CRS-R increased in MCS group from 14 to 17 (p=0.0001) and did not change in the UWS group. One MCS patient improved to eMCS. No differential susceptibility to treatment effect in MCS group in relation to etiology. Improvement of CRS-R in 86% of MCS cases by mean of 2.1 points. No adverse events related to intervention.	Total study - Q1: y Q2: y Q3: y Q4: n Q5: y Q6: n.a. Q7: n.a. Q8: n.a. Q9: n.a. Q10:n.a. Q11: nc Q12: n Q13: nc Q14: y	0	2 weeks of 20 Hz rTMS to left angular gyrus led to an increase in CRS-R in 86% of MCS patients, which was not observed in UWS patients. One patient emerged from MCS. The intervention was reported to be safe with no adverse events. Main weakness is the lack of a control group. In conclusion, 2 weeks of rTMS is associated with an improvement of CRS-R in patients with MCS but not with UWS. It is unclear whether this effect is attributable to rTMS or to the rehab protocol or to natural course.

Table: 40 PICO: 5 Intervention: Transcranial Magnetic Stimulation (TMS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.5.-(1)	Liu et al. Front Neurol 9:982 (2018) Randomized, Sham-controlled Crossover trial OCEBM Level of Evidence (2011) **2**	20 Hz rTMS to left M1 region for 5 sessions with 1000 pulses. One week of wash-out phase then switch to other condition (from real to sham or from sham to real) for 5 sessions.	During Sham condition, the TMS coil was pointed away from the patient	7 patients (2 UWS, 5 MCS) with TBI in 5 patients, HIE and ICH in the other 2. Time since injury from 1 to 6 months. Median age 48 +/- 17 years.	CRS-R at baseline, after first treatment phase (real / sham) and 48h after second treatment phase. In addition, resting state fMRI at same time points with analysis of functional connectivity (FC).	Clinical outcome: There was no rTMS effect on the group level on CRS-R measurements. CRS-R changed after real rTMS from mean 10 points to 11 points after stimulation. On the individual level, one MCS patient with TBI 1 month prior to the study improved with real rTMS from 15 to 23 CRS-R points. Functional Connectivity: There was no clear effect of rTMS on FC on the group level. No adverse events related to intervention.	Total study: + Q1: y Q2: y Q3: y Q4: n Q5: y Q6: y Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: y Q14: y	-1	5 sessions of 20 Hz rTMS to left M1 region did not have an effect on CRS-R on the group level. One traumatic MCS patient emerged from MCS after 5 sessions of rTMS. The intervention was safe. Main weaknesses of the study are the low patient number, the short treatment period and the cross-over-design with short follow-up. There is no indication of rehab treatment. In conclusion, real rTMS but not sham rTMS was associated with regaining of consciousness in one individual patient but not in the overall study population.

Evidence tables for single studies investigating **Deep Brain Stimulation (DBS)** in people with DoC **(PICO-5)**

Table: 41 PICO: 5 Intervention: Deep Brain Stimulation (DBS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures (Follow-up period	Main results (	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.6.-(2)	Lemaire et al. (2018) Annals of Clinical and Translational Neurology OCEBM Level of Evidence (2011) **2**	Deep Brain Stimulation Bilateral, 30Hz-low Frequency, dual pallido-thalamic targeting blinded 1,5 month ON period, 5month stimulation unblinded	Blinded, 1,5 month crossover, OFF period	five adult patients MCS or UWS, >6months after cerebrovascular accident or >1 year after TBI Exlusion: anoxic, N=36 screened N=23 assed for eligibility, selected 5, 3 female, (1xUWS, 4xMCS-) single centre	Baseline 2month Surgery titration 1 month Blind random crossover 1.5month (ON/OFF) ublinded 5month stimulation Primary Outcome: CRS-R Secondary Outcome: Brain metabolism variation to BL with FDG PET Statistics :Random effect models	Two male patients (MCS/UWS) improved CRS-R vs. baseline in subscores (auditory, visual, oromotor/verbal subscore) Increased metabolism in two responders P1: 6.1±1.3 BL DBS ON 8.4±1.8 (vs BL) CO-ON 7.3 ±1.9 CO-OFF 8.6 ±2 P2:	Total study: + Q1: y Q2: y Q3: y Q4: y Q5: y Q6: y Q7: y Q8: y Q9: y Q10: y Q11: y Q12: y Q13: nc Q14: n	0	Limited clinical benefit in 2 patients, mainly visual and auditory. In responders medial cortex activity increase related to internal awareness. No adequate reporting of statistical methods, no CI. 2 patients with sig. differences between ON/OFF Phase, one better one worse. Unfavourable benefit/harm ratio.

Table: 42 PICO: 5 Intervention: Deep Brain Stimulation (DBS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.6.-(3)	Schiff et al. (2007) Nature Single Case Report with multibaseline design OCEBM Level of Evidence (2011) **4**	DBS electrodes bilaterally into central thalamus 6 month double blind crossover within subject trial DBS was alternatingly turned on/off every 30 days after titration phase of 18 weeks In addition: comprehensive rehab program	No control intervention in other patients. Within-subject control in terms of stimulator on/off	Singe subject, 38year old male, in MCS due to TBI for 6.5 years	Repeated CRS-R over a three week baseline; Ability for object naming, purposeful upper extremity limb movement, oral feeding	Significant improvements during on-phases compared to off-phases for arousal, limb control, oral feeding	Total study: + Q1: n Q2: y Q3: y Q4: y Q5: y Q6: y Q7: n Q8: n.a. Q9: y Q10: y Q11: y Q12: y Q13: nc Q14: y	0	Very well conducted single case study with rigorous methods. Highly selected case showing potential of DBS in a patient in chronic MCS after TBI to improve meaningful behaviour. This case serves as a single proof-of-principle suggestion; further studies required.

Evidence tables for single studies investigating **Spinal Cord Stimulation (SCS)** in people with DoC **(PICO-5)**

Table: 43 PICO: 5 Intervention: Spinal Cord Stimulation (SCS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.6.8.-(2)	Xu et al. (2019) Neuromodulation Cohort study OCEBM Level of Evidence (2011) **4**	Epidural (invasive) spinal cord stimulation dorsal column C2-C4 2,5 – 3,5 mA (under individual level for expression of pain) 60 Hz 0,2 msec pulse width 15 min on vs. 5 min off for 12 hours daytime	no sham control	12 UWS patients age 26-65 years TBI: 6 anoxic: 5 hemorrhage: 1 time since lesion 3-24 months Follow-up 11.1 months	CRS-R at Baseline and Follow-up	CRS improved from 6.25 at baseline to 10.8 points at FU. Achieved “responsive” outcome: 5 (3 eMCS. 2 MCS) unresponsive: 7 (1 death)	Total study: - Q1: y Q2: y Q3: y Q4: y Q5: n Q6: n Q7: n Q8: n Q9: n Q10: n Q11: n Q12: n Q13: n Q14: n	0	No improvements in more than half of sample Recovery rate not above spontaneous recovery Risk of pain and stressful procedures

Evidence tables for single studies investigating **Other Interventions** in people with DoC **(PICO-6)**

Table: 44 PICO: 6 Intervention: Near-Infrared Laserstimulation/ Focused Shock Wave Therapy

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1, 0,-1)	Conclusion / Comment
2.7.1.-(1)	Werner, Byhahn & Hesse (2016) Restorative Neurology and Neuroscience OCEBM Level of Evidence (2011) **3-4**	frontal near-infrared laser stimulation (N-LT) 6 Joules for 10 minutes 5 times per week over 4 weeks versus transcranial focused shock wave therapy (F-SWT) 6 Hz, 4000 waves 3 per week over 4 weeks	none all received regular therapy appointments from 10 to 20 per week	n = 8 (N-LT) n = 8 (F-SWT) UWS (14) MCS (2) age 55 ± 20 years time since lesion > 12 months	CRS-R SMART Barthel Index FOUR scale before, week 2 – 4, follow-up at week 8	baseline range CRS-R: 4-10 follow-up-range: 9-16 significant improvement on all scales during intervention in all subjects (except the 3 hypoxia-cases) with no group difference at 4-week-follow-up sustained improvements one patient suffered epileptic seizure	Total study: - Q1: y Q2: y Q3: y Q4: y Q5: n Q6: y Q7: y Q8: n Q9: y Q10: y Q11: n Q12: n Q13: n Q14: n	0	improvements might be result of general stimulation – without sham intervention no decision about specific effects of treatment possible risk of epileptic seizures ? possible discomfort low relevance for clinical practice stimulation effects on level of consciousness unclear

Table: 45 PICO: 6 Intervention: Hyperbaric Oxygen Therapy (HBOT) (in combination with SCS)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.7.2-(1)	Liu J-T. et al., 2009, prospective Case-control study (control from another research group) Surg Neurol OCEBM Level of Evidence (2011) **4**	cervical spinal cord stimulation (cSCS) with 4 implanted electrodes from C2 to C4 with alternating 15 minutes on (1.0-4.7 V; 60-100 Hz) and 15 minutes off for 14 hours during daytime for 1 year in combination with hyperbaric oxygen therapy (HBOT: 2.5atm for 90min.) with 60 sessions (5/week for 4 weeks, then 1 week rest) for the first 3 months after enrolment in combination with daily physical therapy (dosis not reported)	median nerve stimulation (details of control intervention not reported) in combination with daily physical therapy (dosis not reported)	patients in coma (GCS < 11), who had received median nerve stimulation for 3 months Intervention: n=12 (8m, 4f; age: 29+/-9 years; coma duration: 459+/-763 days; min: 132days, max. 2875 days; TBI: 9; median GCS: 9) Controls: n=12 (8m, 4f; age: 36+/-13 years; coma duration: not reported; TBI: 4; median GCS: 8)	Outcome measures: GCS coma score, PVS coma score, brain SPECT (details not given) Follow-up: 1 year planned (details not reported)	For GCS: In the Intervention Group 6/12 patients (50%) reached full GCS (15 points) after 64 to 156 days of treatment; at group level GCS increase from 8.75 at baseline to 12.17; p=0.005 In the Control Group 0/12 patients (0%) reached full GCS; at group level GCS from 8.03 to 8.00, p=0.759 For SPECT: significant increase in cerebral perfusion in intervention group but not in control group	Total study: -- Q1: n Q2: n Q3: n Q4: y Q5: n Q6: n Q7: n Q8: n Q9: n Q10: n Q11: y Q12: y Q13: nc Q14: n	0	cSCS in combination with HBOT led to emergence from coma in 50% of chronic DOC patients, when treated for 1 year. The control intervention (median nerve stimulation) is not described at all and the control group differs in etiology (less TBI) and important information is not given (e.g. duration of coma). There is very substantial risk of bias. The results seem promising but relevance for clinical practice remains unclear.

Table: 46 PICO: 6 Intervention: Hyperbaric Oxygen Therapy (HBOT)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.7.2.-(2)	Sankaran R. et al., 2019 Neurol India ; Case-control study OCEBM Level of Evidence (2011) **4**	20-60 sessions HBOT with 100% O_2 at 2 atm. for 1 hr. each	"Standard care" including physical therapy and simulating medication	25 HIE patients 1-12 months after cardiac arrest in a neurorehab facility; CRS-R < 7 at enrollment HBOT: n=9; 38+/- 11 yr; controls 40 +/- 14 yr	Outcome measures: CRS-R, DOC scale, Karnofsky performance scale (KPS) Follow-up: up to 12 months	At 4-8 months CRS-R was higher in HBOT group (7.7 vs. 3.8) At 9-12 months not sufficient data was provided to perform sensitivity analysis There was no difference in KPS Harm: increased respiratory secretion in HBOT	total study: -- Q1: n Q2: n Q3: y Q4: y Q5: n Q6: n Q7: n Q8: nc Q9: n Q10: n Q11: n Q12: n Q13: n Q14: n	-1	Very low quality Case-Control-Study with very high risk of bias. Details about population not given in detail; publication does not permit to fully understand the study protocol and outcome measuremens. No relevance for clinical practice due to severe methodological weaknesses.

Table: 47 PICO: 6 Intervention: Hyperbaric Oxygen Therapy (HBOT)

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.7.2.-(3)	Sahni T et al., 2012, Br J Neursurg Retrospective Case-control study OCEBM Level of Evidence (2011) **4**	HBOT with at least 30 sessions at 1.5 ATA for 60 min. once daily in addition to "standard care".	"Standard care" (details not reported)	TBI patients, who received at least 30 x HBOT (no further inclusion criteria reported) Intervention: n=20 (13m, 7f; age: 17-51 years; 15 patients in UWS; GCS 2-10; 15 patients with time since injury >1->6 months Controls: n=20 (16m, 4f; age: 19-53; GCS: 3-10; 156 patients in UWS; time since injury 18 patients with > 1 ->6 months)	Outcome measures: Disability Rating Scale (DRS); Ranchos Los Amigos Scale RLAS) Follow-up: not reported	HBOT group: DRS improved in the 10 patients, who were in UWS for at least 1 month from 23.3+/-3.22 to 17.25 +/-5.04 (for patients 1-6 months post injury); 6 of the 10 patients improved beyond UWS. Control group: 14 patients had been in UWS for more than 1 month. DRS improved in that group from 23.38+/-2.43 to 21.92+/-3-4. At the end of the follow up, 10 patients were still in UWS. Statistical tests for significance of changes / group differences were not performed.	Total study: -- Q1: n Q2: n Q3: n Q4: n Q5: n Q6: n Q7: n Q8: y Q9: nc Q10: nc Q11: n Q12: y Q13: nc Q14: n	0	HBOT was associated with emergence from UWS in 60% of TBI patients, who had been in UWS for > 1 month and in 29% of control patients. There is very substantial risk of bias and results are difficult to interpret because important data/details are missing (type of standard therapy, length of follow-up). The results seem interesting but relevance for clinical practice remains unclear.

Table: 48 PICO: 6 Intervention: Transplantation of Fetal Cells

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.7.3.-(1)	Seledtsov V.I. et al. 2006 Bull Exp Biol Med Retrospective case-contro study OCEBM Level of Evidence (2011) **4**	-tissues from human fetuses (12-22 week) -cell suspension -cells cryopreserved in liquid nitrogen -cell defrosted on the day of transplantation --injected into suparachnoidal space	No control inervention	25 patients (8f, 17m) Age 18-63 GCS 3-5 -15 pat. (diffuse axonal injury) in 11/15 combined with hematoma; -10 pat. Severe compression of the brain 5-8 weeks post trauma Control group retrospectively selected at random for comparison with each patient of the main group	- Karnovsky scale -clincal symptoms	-awaking syndrome 3-5 days after injection -after 7-12 days starting communication -after 15-20 days recovery of mental function -Karnovsky scale after 1,5 years significant increase Mortality in intervention group 8% vs. 56% in historic cotrol	Total study: -- Q1: n Q2: n Q3: n Q4: n Q5: y Q6: n Q7: n Q8: n Q9: n Q10: n Q11: n Q12: n Q13: n Q14: n	-1	Extreme methodical weaknesses with extreme risk of bias. No specific DoC scale used. Unclear whether new population or the one published by same group in 2005 (2.7.3.-(2))

Table: 49 PICO: 6 Intervention: Transplantation of Fetal Cells

Ref. no.	Author, year, study type, evidence level	Intervention	Control intervention	Population	Outcome measures Follow-up period	Main results	Validity rating (++ + - --) (Q1-Q14)	Relevance for clinical practice (2,1,0,-1)	Conclusion / Comment
2.7.3.-(2)	Seledtsov V.I. et al. 2005 Biomed Pharmacother retrospective cohort study OCEBM Level of Evidence (2011) **4**	-tissues from human fetuses (brain, liver; 16-22 week) -cell suspension -cells cryopreserved in liquid nitrogen -cell defrosted on the day of transplantation --injected into suparachnoidal space via lumbar puncture N=25: 1 injection N=12: 2 injections N=1: 3 injections	No control intervention; case-matched control group	At least 5-8 weeks post injury 38n (10f; 28m) TBI average age 38 (19-60) GCS 4,1-4,6 Control group 38n (9f; 29m) average age 38 (19-60) GCS 4,1-4,6	- GCS 18-24 month	"Good" outcome in 47% of intervention group vs. 0% of control group ($p<0.001$) 33n -awaking syndrome 3-7 days after injection -after 5 days starting communication -after 15-20 days recovery of mental function 3n: -remission 2n: Dead After 4-6 years 20 n went back to work	Total study: + Q1:- Q2:- Q3:-- Q4:- Q5:+ Q6:- Q7:- Q8:- Q9:- Q10- Q11:- Q12:- Q13:- Q14:-	0	Extreme methodical weaknesses with extreme risk of bias. No specific DoC scale used. Only matched control group. Many details on clinical condition missing

Evidence Tables for Metaanalyses and Systemic Reviews

Validity assessment (adapted from AMSTAR-2): yes (y), partially yes (py) [not all, but "essential features" yes], no (n), not clear (nc), or not applicable (na)

1. Were review methods established prior to the conduct of the review (written protocol)?
2. Were research questions clearly phrased, e.g. did selection criteria for the review include the components of PICO, and clinically meaningful?
3. Was the study design selection of included trials adequate for the research question?
4. Did the review authors use a comprehensive literature search strategy (data bases, key words, justify search restrictions [e.g. language])?
5. Were all processes (screening, selection, assessment risk of bias, data extraction) performed in duplicate?
6. Did the review authors describe the included studies in adequate detail (compare PICO)?
7. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
8. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results, and was it meaningful to combine the studies selected for meta-analyses?
9. Have all clinically relevant effects of the intervention(s) of interest (benefit, including long-term effects; harm; acceptability) been addressed?
10. Did the review authors assess the potential impact of RoB in individual studies and of publication bias on the results of the meta-analysis or other evidence synthesis and discuss the implications of the findings of their assessment on the estimates of therapeutic effects as reported?
11. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
12. Did the review authors report any potential sources of conflict of interest (CoI), including any funding they or the authors of included studies received for conducting the review or their studies? If a risk that CoI might have influenced the review's result is not unlikely, was its management described (for the review or the trials included) and adequate?
13. Do the results sufficiently support the conclusions drawn?

Evidence tables for **Systematic Reviews** for **Positioning** in people with DoC **(PICO-3)**

Table: 50 PICO: 3 Intervention: Positioning

Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0,-1)	Conclusion
2.4.1.-(1)	Ng & King 2021 OCEBM Level of Evidence (2011) **1** (SR of RCTs and observational studies)	10 Studies with 264 participants	2020-06- 21 Medline, CINAHL, AMED & The Cochrane Library. Search algorithm not reported in publication or protocol	Adults of either gender with diagnosis of coma, UWS or MCS)	All common variations of tilt table devices and standing frames were searched for. Appropriate comparison was with traditional physiotherapy, physical therapy treatments or differing head-up tilt devices.	The primary outcome of interest was change in consciousness as measured by neurobehavioural assessment, or physiological change linked to consciousness. Articles were included if they evaluated consciousness using an appropriate outcome measure on this population undergoing head-up tilt treatment.	*No Meta-analysis performed* Post-intervention (single intervention): t=2 (case-series): Cohen's d 0.367 to 0.868 Wessex Head Injury Index t=1 (case-series): time eyes open +298% prop. Change t=2 (case-series, RCT): insufficient data Post-intervention (treatment regimen) t=2 (prosp. Cohort study) GCS: 41 to 47% prop. Change t=3 (RCTs) GCS-R: d=1.934 to 1.996	Validity: + Q1: y Q2: y Q3: y Q4: y Q5: y Q6: y Q7: y Q8: na Q9: n Q10: y Q11: y Q12: y Q13: y,	2	Quote: "*There is, as yet, insufficient evidence to require the use of the head up tilt to raise consciousness in a prolonged disorders of consciousness population. Head-up tilt using an Erigo reduces the occurrence of orthostatic hypotension in a prolonged disorder of consciousness population*." Formal outcome measures clinically relevant with clinically relevant magnitude of effects in RCTs No results regarding benefit-harm-ratio and acceptability. Current research is of rather high risk of bias, RCTs are scarce Measures are imprecise and there is heterogeneity (qualitative measured) findings are relevant for clinical practice

Evidence tables for **Systematic Reviews** for **transcranial Direct Current Stimulation (tDCS)** in people with DoC **(PICO-5)**

Table: 51 PICO: 5 Intervention: tDCS

Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0,-1)	Conclusion
2.6.1.-(1)	Feng et al. 2020; Rev Neurosci OCEBM Level of Evidence (2011) **1**	14 studies on noninvasive brain stimulation (NBIS): 3 rTMS, 1 tRNS, 10 tDCS), either single session 20 min (n=3), 5 sessions 10 min (N=1), 5 sessions 20 min (n =4) or 10 sessions 20 min (n=2) Subgroup analysis of 6 RCT with anodal vs. sham tDCS of the left DLPFC (5 (4 cross over, 2 parallel design)	Search date: 1.1.2000-15.2.2020; Databases: PubMed (206), EMBASE (301), Web of Science (306); Cochrane Central Register of Controlled Trials (72); Keywords: noninvasive brain stimulation; tDCS, tACS; Conditions DOC, UWS, VS, MCS, coma; Selection according to PICOS and RCTs	<u>Subgroup analysis:</u> <u>Study 1 (Thibaut 2014):</u> crossover design; 25 UWS: 1 month – 19 years duration; etiology: 6 TBI, 18 nTBI, 1 mixed; age 17-73 years (mean 42 years); 30 MCS: 10 days – 26 years duration; Etiology: 19 TBI, 10 nTBI, 1 mixed; age 15-85 years (mean 43 years). <u>Study 2 (Thibaut 2017:</u> crossover design; 16 MCS only; 5-365 months duration; 11	<u>Subgroup analysis:</u> 4 trials cross-over design (1 trial with single session 20 min (Thibaut 2014); 2 trials with 5 sessions 20 min each (Estreano et al., Thibaut et al. 2017), 1 trial with home based tDCS over 4 weeks and 8 weeks washout (22 patients received 16-20 active stimulatios (Martens et al. 2018); 2 trials with parallel design: 10 sessions over 14 days, 20 min each (Zhang et al. 2017, Wu et al. 2019); All trials: 2 mA anodal stimulation of DLPFC; 5 left, 1 left or right (Wu et al.). All trials: 2 mA an	All studies used the CRS-R as the main clinical outcome measure. Further surrogate outcome measures were reported in 2 studies (EEG baseline activity (Estreano 2017), P300 in oddball paradigm (Zhang 2017), functional EEG connectivity by phase locking value (Wu 2019).	The metaanalysis of ^1 studies (rTMS and tDCS, N=182) showed a significant positive effect of NIBS on the CRS-R (effect strength was estimated by Hedges g= 0.522, p < 0.0001) Risk of publication bias was evaluated by Egger's test and showed no evidence for publication bias (p =0.72). Subgroup analysis of stimulation protocol showed a significant effect of left DLPFC anodal tDCS on CRS-R compared to sham (N=98 UWS and MCS, Hedges g=0.703, p<0.001, Egger's test p=0.66), no significant effects were found for studies using anodal tDCS on the motor cortex (Martens et al. 2019), right DLPFC (Wu et al. 2019), and posterior parietal cortex (PCC) (Huang et al. 2017), as well as high-frequency tRNS to bilateral DLPFC (Mancuso 2017). Subgroup analysis of anodal tDCS on left DLPFC	Quality of RCTs assessed with PEDro (all studies ≥ 7) Validity + Q1: y Q2: y Q3: y Q4: y Q5: y Q6: py Q7: y Q8: y Q9: n Q10: y Q11: y Q12: n Q13: y	1	The metaanalysis of NIBS on CRS-R over all patients and applied techniques indicated a significant positive effect. The subgroup analysis of 6 studies with an almost identical stimulation protocol indicates that this effect was primarily driven by a positive effect of anodal tDCS on left DLPFC No significant effect of anodal tDCS on right DLPC or primary motor cortex or in UWS patients could be observed. This meta-analysis does find evidence for an positive effect of anodal tDCS on the left DLPFC in MCS patients. The main weakness is the intrinsic hetereogeneity of the population, especially the duration since brain injury, location and etiology of brain injury), as well as the low and unbalanced number of patients, short follow-up period and missing data on long term outcome. Generally, the crossover-design of the majority of studies makes

				TBI, 5 nTBI; age 17-74 years (mean 47 years). <u>Study 3 (Zhang 2017):</u> parallel design; 13 tDCS (5 UWS, 8 MCS, 5 TBI, 2 anoxia, 5 hemorrhagic stroke, 1 ischemic stroke); 13 sham (6 UWS, 7 MCS, 7 TBI, 3 anoxia 2 hemorrhagic stroke, 1 ischemic stroke), 1-17,4 months duration; age 27 – 85 years. <u>Study 4 (Wu 2019):</u> parallel design; 10 tDCS (6 UWS, 4 MCS), 5 left DLPC (2 UWS, 3 MCS; 3 ICB, 2 TBI); 5 right DLPFC (4 UWS, 1 MCS; 4 ICB, 1 TBI); 5 sham (2 UWS, 3 MCS); 21-631 months duration (duration tDCS group 42-631 months; age 16-77 years; duration sham group 21- 174			showed an significant positive effect on CRS-R in MCS patients only (N=70 crossover plus N= 14 parallel design, Hedges g= 0.851, p<0.001, Egger's test p=0.49) but not in UWS (Hedges' g=0.102, p=0.784) A meta-regression analysis of a potential stimulation-dose effect of left DLPFC anodal tDCS showed no significant effect over all patients (p=0.95) and MCS patients (p=0.38)			interpretation difficult for lack of true controls. At the same time the interpretation of the parallel design studies is limited by hetereogeneity and small size of the compared populations. Overall the meta-analysis is valid and of high quality. At some points, data differ from original publications, though.

				months; age 34-59 years). Study 5 (Estraneo 2017): Cross-over; 7 UWS, 6 MCS; 3-84 months duration; 18-83 years; etiology: 1 TBI, 6 anoxic, 6 vascular. Study 6 (Martens 2018): cross over, 27 MCS, 10 months – 14 years duration; age 17-70 years; 12 TBI, 10 anoxia, 5 vascular.						

Evidence tables for **Systematic Reviews** for **Deep Brain Stimulation (DBS)** in people with DoC **(PICO-5)**

Table: 52 PICO: 5 Intervention: DBS

Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0,-1)	Conclusion
2.6.6-(1)	Vanhoecke & Hariz (2017) Brain Stimulation, 10 OCEBM Level of Evidence (2011) **1**	Systematic review 19 studies Total of N = 79 (VS = 68, MCS = 11)	2017 PubMed Embase Medline Web of Science French and English articles from 1968 to March 2017	age 15-75 female 20 male 33 rest n.a. TBI Anoxic Vascular Interval since lesion 2 months – 10 years	DBS uni- or bilateral thalamic nuclei formatio reticularis	CRS-R GOS	emergence from VS to MCS in single cases, most patients did not improve higher scores on scales but in most cases no consistent consciousness or communication	Validity: + Q1: y Q2: y Q3: y Q4: y Q5: n Q6: y Q7: n Q8: n Q9: y Q10: y Q11: y Q12: n Q13: y	0	no valid results, no double-blinded studies so far, further investigation of method needed marginal effects, minor functional gains general stimulation effects in longtime therapeutically neglected individuals very probable ethical issues

Evidence tables for **Systematic Reviews** for **Median Nerve Stimulation (NMS)** in people with DoC **(PICO-5)**

Table: 53 PICO: 5 Intervention: NMS

Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0,-1)	Conclusion
2.6.7.-(1)	Meyer et al. (2010) OCEBM Level of Evidence (2011) **1**	Systematic review 2 RCT 1 case series N = 22	2008 Cinal Embase Medline PsycInfo published 1980-2008	age 13-66 female: 6 male: 10 rest: n.a.	MNS vs. sham biphasic pulses of 20 mA at 40 Hz with 20 sec/minute	GCS GOS FIM	increased blood flow and improved EEG-activity faster emergence from coma shorter time on ICU	Validity: + Q1: y Q2: y Q3: y Q4: y Q5: n Q6: n Q7: n Q8: n Q9: y Q10: n Q11: y Q12: n Q13: y	0	interventions started within first two weeks after brain injury results do not reach statistical significance

Evidence tables for **Systematic Reviews** for **Spinal Cord Stimulation (SCS)** in people with DoC **(PICO-5)**

Table: 54 PICO: 5 Intervention: Spinal Cord Stimulation (SCS)

Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0,-1)	Conclusion
2.6.8-(1)	della Pepa et al. (2013) Stereotactic Funct Neurosurg OCEBM Level of Evidence (2011) **1**	Systematic review 10 papers N = 308	Medline English and Japanese publications from 1988 to 2013	age 19-75 3-53 months since injury	SCS dorsal column at C2-C4 Cyclic mode on/off without reaching motor threshold 2-15 V 25-100 Hz Pulse width 0,3-1 ms 2-11 hours/day	Clinical improvement GCS CBF	responders 51,6% (amelioration of function and arousal) effects within days versus months	Validity: + Q1: y Q2: y Q3: y Q4: n Q5: y Q6: y Q7: n Q8: n Q9: n Q10: n Q11: y Q12: n Q13: n	0	clinical parameters not clear, risk of bias with lack of valid scales for clinical improvements benefit-harm-ratio not discussed no sham-controls

Evidence tables for **Systematic Reviews** for **Other Interventions** in people with DoC **(PICO-6)**

Table: 55 PICO: 6 Intervention: Transplantation of Fetal Cells

Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0,-1)	Conclusion
2.7.3.-(3)	Cossu G. ; 2013 ; Br J Neurosurg OCEBM Level of Evidence (2011) **1** (SR of RCTs)	Review covers hyperbaric oxygen therapy (HBOT) and cell therapy (CT) HBOT: no sufficient details reported CT: 2 controlled retrospective trials reported. Combined: 63 DoC patients vs. 63 controls	Until 09/2011 Pubmed, Embase, Ovid, Cochrane Key words: therapy, “post traumatic coma”, “coma arousal”, “head injury”, “brain injury”, HBOT, CT	GCS < 8 5-8 weeks post TBI no further details given	The SR addresses several interventions. In this table the exclusive focus is on HBOT or CT For CT: CT vs. rehabilitation therapy, 5-8 weeks after TBI	Awakening, GOS, mortality, atrophy in MRI	Trial 1: CT improved outcomes by factor 2.5; no SAE 33/38 patients showed “awakening” after 3-7 days, restoration of “main psychical functions” at 15-20 days post-grafting Mortality in CT group 5% vs. 45% in controls Trial 2: Mortality in CT group 8% vs. 56% in control group; awakening Reduction of atrophy after 1-1.5 years	Validity: -- Q1: nc Q2: n Q3: nc Q4: y Q5: n Q6: n Q7: n Q8: na Q9: n Q10: n Q11: n Q12: n Q13: nc	0	For interventions HBOT and CT: Low quality review with low validity and high risk of bias. Little detail is given for individual studies. No conclusions for HBOT. For CT 2 trials from the same group are reported, which show potential benefit of CT in patients with GCS < 8, 5-8 weeks after TBI. Little information about harm associated with intervention. SR is not suitable to answer PICO – analysis of single studies is necessary

Evidence tables for **Systematic Reviews** for **Other Interventions** in people with DoC **(PICO-6)**

Table: 56 PICO: 6 Intervention: Acupuncture

Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0,-1)	Conclusion
2.7.4.-(1)	Li Tan et al.; 2019 ; Evid Based Complement Alternat Med OCEBM Level of Evidence (2011) **1**	49 controlled trials reported including 3511 patients. 1800 participants in the acupuncture group and 1711 in the control group	Until 02/2018 PubMed, Cochrane Library, Chinese Biomedical Literature Database (CBM), VIP, WanFang Database, and Chinese National Knowledge Infrastructure (CNKI) Key words reported	Only TBI pat., high heterogeneity generally. Duration highly heterogeneous 7 days -3 months, sometimes unclear Not enough further details given	Acupuncture 18, electroacupuncture 16, acupuncture combined with HPO (hyperbaric O2) in 6, acupuncture combined with TCM in 7 Control groups without acupuncture No sham acupuncture, therefore most likely biased results	Improvement in consciousness, mortality outcome results by difference in GCS or GOS (GOS 1-2 = low consciousness)	Statistically significant difference between the acupuncture and the control groups (RR=1.48, 95%CI: 1.40 1.56, Z=13.49, and P<0.00001) Authors conclude: These positive fndings should be interpreted cautiously due to the high risk of bias in all of the included studies, the quality of which was poor overall	Validity: -- Q1: y Q2: nc Q3: n Q4: y Q5:y Q6: n Q7: y Q8: nc Q9: n Q10: y Q11: n Q12: n Q13: y	0	Authors: Although the results suggest that acupuncture produced superior effects on the recovery of consciousness in the included trials, the limitations make this questionable and diffcult in drawing definitive conclusions. The review tries to follow adequate standards, however did include too many studies of low quality SR is not suitable to answer PICO – analysis of single studies is necessary

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Ref.-Nr.	Author, year, level of evidence	Study type, number of studies, number of participants	Search date, searched databases, search algorithm	Population	Intervention and Control intervention	Outcome measures Follow-up period	Main results Risk of bias	Validity rating (++ + - --) (Q1-Q13)	Relevance for clinical practice (2,1,0, -1)	Conclusion
2.7.4.-(2)	Zhang et al. 2020. Altern Ther Health Med. OCEBM Level of Evidence (2011) **1**	24 RCTs, including 1538 participants All studies in Chinese	Until 1. March /2018 Medline, Embase, CENTRAL, and 4 Chinese medical databases without language restrictions. included RCTs that examined acupuncture as a therapy for arousing patients in a coma after TBI. Key words: Acupuncture, Acupuncture ear,electro acup., meridians, acup. points, craniocerebral trauma, brain edema, GOS, GCS, unconsciousness, cerebrovascular trauma	Little information on populations, people of any age and either gender Duration of symptoms only in 2 studies beyond 30 days, 15 studies withous information on duration of symptoms	Acupuncture once daily (20) 1 with HO, 3 studies with unclear frequency, Control intervention:: conventional treatment (unspecified) No sham acupuncture	GOS, GCS, wake-promoting rates (no definition given) Comparison after 1 month of treatment – or given timepoint closest to 1 month	No adverse events reported GOS (RR, 1.95, 95% CI [1.64 to 2.31], P < .01; I^2 = 0%), wake-promoting rates (RR, 1.48, 95% CI [1.19 to 1.83], P < .01; I^2 = 52%), and GCS (MD, 1.78, 95% CI [1.10 to 2.45], P < .01; I^2 = 52%) .	Validity: -- Q1: n Q2: n Q3: n Q4: y Q5: y Q6: n Q7: nc Q8: nc Q9: nc Q10: y Q11: n Q12: n Q13: y	0	The review showed a positive acupuncture effect. However, the low quality, unclear measurements and lack of sham treatments do not allow a recommendation. There is no study answering the precise PICO question. No definition of coma is addressed. Time window since lesion is too early or unknown.

12.10.2023: Gültigkeit der Leitlinie nach inhaltlicher Überprüfung durch das Leitliniensekretariat verlängert bis 30.06.2024

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