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| Table 1a. Pharmacological intervention summaries |
| **First author** | **Year** | **Country** | **Study Design** | **Intervention** | **Inclusion**  | **Exclusion** | **Demographics** | **% TBI** | **Assessment** | **TBI specific Findings** |
| Johansson et al. | 2014 | Sweden | Randomized (Latin Square Design) cross over design | **Target** Fatigue & Pain**Intervention**Methylphenidate**Frequency**Low dose: Week 1: 5mg X 1; week 2: 5mg X 2; weeks 3 and 4: 5mg X 3. Normal dose: Week 1: 10 mg X 2; week 2: 20 mg + 10mg + 10 mg; week 3: 20 mg + 20 mg + 10 mgand week 4: 20 mg X 3.**Control**No MedicationLow Dose | * Age: 18–65
* Mental fatigue and pain due to
* head trauma >12 months earlier/ diagnosed with post-concussion syndrome
* GOS(E) >5
* Healthy pre TBI
* No language and motor problems
* At study start each person had reached a steady state level concerning social and functional performance
 | * Pain was the main problem or high degree of somatization
* Major psychiatric disorder such as depression
* Organic personality disorder or other organic CNS disorder.
* Heavy analgesic medication with risk of interaction with methylphenidate treatment
* Women of child-bearing age not on contraceptives.
* Pregnant women.
* Alcohol or drug abuse.
* Untreated cardiovascular disease
 | N = 24Male – 12Female – 12Age – 38.6 (11.1)Ethnicity not reported | 100%Mild TBI - 23Moderate TBI – 1  | Mental Fatigue Scale (MFS) | Significant improvement (F= 21.7, p=0.001) with treatment. |
| Johansson et al. | 2015 | Sweden | Randomized (Latin Square Design) controlled trial | **Target**Mental Fatigue, Pain and Cognitive Functions**Intervention** Methylphenidate**Frequency**Low Dose: Week 1: 5mg X1; week2: 5mg X2; week3 and 4: 5mg X3. Normal dose: Week1: 10 mg X2; week2: 20mg + 10mg + 10mg; week3: 20mg + 20mg + 10mg and week4: 20mg X3 **Control**No MedicationLow Dose | * Age 18-65 years
* Fatigue and pain due to head trauma for >6 months
* GOS >5
* No language and motor problems
 | * Pain as main problem
* Previous major psychiatric or organic disorder
* Child-bearing age not taking contraceptives,
* Pregnant women,
* Alcohol or drug abuse
* Untreated cardiovascular disease
 | N = 44Male – 19Female – 25No medication group – 14Low dose group – 15Normal does group – 15Age – 38.9 (10.8)Ethnicity not reported | 100% mild TBI | Mental Fatigue Scale (MFS) | No Medication21.7(6.3)Low Dose =18.3(5.6)Normal Dose =14.0 (4.8)F=20.198, p<0.001Significant differences reported for no medication vs low and normal dose, and low dose vs normal. |
| Johansson et al. | 2017 | Sweden | Follow up | **Target**See prior study**Intervention**Methylphenidate**Frequency**See prior study**Control**See prior study | * Age 18–65 years
* GOS(E) - 5 or better
 | * n/a
 | N = 30 Male – 12 Female – 18Age – 39.7 (12.5)Ethnicity not reported | Moderate TBI – 4Mild TBI – 28 | Mental Fatigue Scale (MFS) | Pre – 23.8 (5.5), post – 14.0 (6.4)Significant within group changes after 6 months (p<0.001) |
| Zhang & Wang | 2017 | China | Double blind placebo control | **Target**Mental sequelae after TBI**Intervention** Methylphenidate**Frequency**flexibly titrated from 5mg/d at the beginning, then gradually increased by 2.5mg/d until reaching 20 mg/d**Control**Placebo | * Age 18-65 years
* Mild-moderate TBI
* Depression w BDI > 18
* MMSE > 19
* 2 weeks-1year post TBI
 | * Multiple trauma that might affect the examination
* Serious diseases, such as cancer
* Abnormal laboratory examinations
* Allergy to any drug
* Treated with neuroleptics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and lithium within 4 weeks
* Involved in other clinical trials in the past 3 months
* Pregnancy
 | N = 36Male – 27Female – 9Ethnicity – Han – 22Hui – 14Intervention N = 18Age – 36.3 (10.9)Placebo N = 18Age – 34.9 (12.1) | 100% | Mental Fatigue Scale (MFS) | Intervention: Pre = 24.5 (5.1), post = 12.1 (4.9)Control: Pre = 25.1 (5.3), post = 17.9 (7.3)Significant group difference was observed after 30 weeks of treatment (p=0.005) |
| Grima et al. | 2018 | Australia | Randomized double-blind placebo controlled two-period two-treatment crossover study | **Target** Sleep Disturbances**Intervention**Melatonin (2mg Circadin)**Frequency**2mg 2hours before initiating sleep for 4 weeks**Control**Placebo | * Age 18-65 years,
* Mild to severe TBI
* Initial GCS 3–14,
* PSQI global score ≥8,
* Diagnosis of chronic insomnia
 | * Self-reported sleep problems,
* Fatigue or neurological conditions pre TBI
* Pregnancy
* Undertaken trans-meridian travel across >1 time zone
* Night shift work in last 3 months
* High risk of obstructive sleep apnea on Berlin Questionnaire
* Used non-prescription sleep meds, benzodiazepines or hypnotics in last 6 weeks
* Used illicit or psychoactive substances in last 12 months.
 | N = 33Melatonin N = 18Placebo N = 15Male – 22Female – 11Ethnicity not reportedAge – 37 (11) | Severe TBI – 28Moderate TBI – 3Mild TBI – 2 | Fatigue Severity Scale (FSS) | Adjusted means for sequence and periodMelatonin treatment =-4.18 (-4.74 to -3.62)Placebo treatment = -3.73 (-4.28 to -3.17)Group differences were observed (p =0.03) |
| Sakellaris et al. | 2007 | Greece | Randomized, prospective, comparative, open-labelled study  | **Target**TBI complications**Intervention** Creatine (Cr)**Frequency**0.4 g/Kg every day for 6 months**Control**No medication | * Age - 1-18 y/o
* GCS 3-9
* Pediatric trauma score (PTS) 4-12
* Administered within 4h from the time of injury
 | * H/o head injury
* Known psychiatric disorder
 | N = 39Age – 1 – 18 yearsCreatinine groupN = 20ControlN = 19Ethnicity not reported | 100% TBI | Fatigue Reported Symptoms | Significant group difference in reported Fatigue: X2(1)= 17.881, p < 0.001 |
| Berginstrom et al. | 2017 | Sweden | Randomized, double-blind, placebo-controlled Trial | **Target**Fatigue**Intervention**Monoaminergic stabilizer (−)-OSU6162**Frequency**5 mg twice a day in week 1, 10 mg twice a day in week 2, and 15 mg twice a day in weeks 3 and 4**Control** Placebo | * Age 18-65
* TBI > 12 months
* GOS-E >5,
* FSS>36
 | * Neuro or psychiatric issue
* Severe dementia
* Alcohol or drug abuse
* Heart, liver, kidney or active neoplastic disease
* Hx of seizures
* Electroconvulsive therapy in last 90 days, clozapine,
* Pregnancy
 | N = 64Male – 37Female – 27Ethnicity not reportedControlN = 31 Age – 42.58 (14.64)Treatment N = 33Age – 41.42 (12.59) | 100% TBI | Fatigue Severity Scale (FSS) | Intervention:Pre = 47.33 (8.98), Post = 40.09 (12.66)Control: Pre = 48.23 (7.95),Post = 42.77 (12.92)No significant group differences were observed, yet significant improvements at follow up was observed (p <.01) |
| Mental Fatigue Scale (MFS) | Intervention:Pre = 18.94 (5.13), Post = 15.76 (5.91)Control: Pre = 17.32 (5.21),Post = 14.4 (5.91)No significant group differences were observed, yet significant improvements at follow up was observed (p <.01) |
| Mossberg et al. | 2017 | USA | Open label growth hormone replacement | **Target**Physical and cognitive functioning after TBI**Intervention** Growth Hormone**Frequency**52 weeks0.2 mg/day for 2 months, then 0.4 mg/day for 2 months, then 0.6 mg/day rest of the study**Control**n/a | * TBI at least 12 months prior to enrollment
* Abnormal GH secretion by glucagon stimulation testing
 | * Premorbid history of a neurological disorder
* Not fluent in English
* Aphasia syndrome
* Inability to complete neuropsychological testing
 | N = 15Male – 10Female –5Age – 45.5 (11.2)Ethnicity – Caucasian -13Hispanic – 1 African-American – 1  | 100% TBI | Fatigue Severity Scale (FSS) | Pre = 44.3 (13.5)Post = 34.0 (12.5)Within group significant improvements (p=0.039) |
| Jha et al. | 2008 | USA | Single center double-blind randomized placebo-controlled crossover design | **Target**Fatigue and Excessive daytime sleepiness**Intervention**Modafinil**Frequency**10 weeks100mg for 3 days, then 200mg for 11 days, then 400mg for 8 weeks**Control**Placebo | * TBI
* At least 1 year post injury
* Experiencing disabling symptoms of fatigue and/or excessive daytime sleepiness
 | * Neurologic or neuropsychiatric diagnoses that would obscure the evaluation of the medication’s effectiveness
* History of other likely causes of EDS
* Concurrent medication and/or clinically significant systemic disease that might cause fatigue and/or diminished arousal
* Epilepsy
* Cardiovascular disease or risks including hypertension requiring medical treatment
* History of severe renal or hepatic impairment
* Significant psychiatric or behavioral disturbance that would obscure the evaluation of medication effectiveness
* Non-English speaking
* Pregnant females or females of childbearing potential unless acceptable double barrier contraceptives were in use.
 | N = 51Male – 35Female – 16Age – 38.25 (12.20)Group AN = 27Group BN = 24Ethnicity –White – 43 Hispanic – 5Black – 2Native American – 1  | Severe TBI – 51%Moderate TBI – 23.%Mild TBI – 25.5% | Fatigue Severity Scale (FSS) | Period 1: Intervention: Pre = 45.22 (11.82)Post = 39.36 (15.61) Follow-up = 37.13 (18.33)Placebo: Pre = 44.46 (12.17), Post = 37.70 (12.55) Follow-up = 36.91 (14.08)Period 2:Intervention: Pre = 38.17 (15.23), Post = 31.38 (10.66) Follow-up = 28.90 (14.03)Placebo: Pre = 35.92 (16.82)Post = 33.74 (16.16), Follow-up = 30.95 (16.25)No group differences observed, although within group improvements observed for both groups. |
| Modified Fatigue Impact | Period 1: Intervention: Pre = 46.56 (19.28), Post = 38.65 (16.09) Follow-up = 35.63 (20.00)Placebo: Pre = 47.17 (15.53) Post = 36.45 (15.03) Follow-up = 33.55 (18.16)Period 2:Intervention: Pre = 39.73 (20.82)Post = 28.91 (19.06) Follow-up = 28.27 (16.06)Placebo: Pre = 36.27 (17.67)Post = 37.74 (17.51), Follow-up = 31.20 (19.44)Mixed results in crossover period. |
| Kaiser et al. | 2010 | Switzerland | Prospective, double-blind, randomized, placebo-controlled pilot study | **Target** – Fatigue and Excessive daytime sleepiness**Intervention**Modafinil**Frequency**100 to 200 mg 6 weeks**Control**Placebo | * Fatigue and/or
* Excessive Daytime Sleepiness
 | * Neurologic, psychiatric or other disorders
* Medication causing sleep-wake disturbances
* Significant sleep-wake disturbances pre-injury
* Chronic sleep deprivation
 | N = 20Male – 17Female – 3PlaceboN = 10Age – 43 (19)Modafinil N = 10Age – 37 (9)Ethnicity not reported | 100% Mild – Severe TBI | Fatigue Severity Scale (FSS) | Modafinil: Pre = 4.6 (0.8), Post(change from baseline) = 0.8 (1.0)Placebo: Pre = 5.0 (1.4) post (change from baseline) = 0 (0.6) Group difference in difference score (p=0.005 Mann-Whitney U); not significant once correcting for sex, age, TBI severity, and Beck Depression and Anxiety Scale. |
| Lequerica et al. | 2015 | USA | Double blind placebo control with a crossover design | **Target** – Sleep and daytime functioning**Intervention**Ramelteon**Frequency**3 weeks – nightly dosage of 8mg**Control**Placebo | * 1 or more of following
* GCS <15
* LOC >5 min
* PTA >30 min;
* Abnormal neuroimaging findings or neurologic deficit after TBI
 | * Abnormal levels of liver enzyme
* Taking Luvox or fluvoxamine,
* Free of know hypnotic agents for 2 weeks
 | N = 13Sex not reportedRamelteon First N = 8Age – 45.3 (19.7)Placebo FirstN = 5Age – 38.2(14.8)Total (N = 13)Age – 42.5 (17.7)Ethnicity not reported | Mild TBI – 7Moderate to severe TBI – 6 | The Brunel Mood Scale: Fatigue | Intervention first: Post = 8.6 +3.6Placebo first: Post = 9.2 + 4.5 Total= 8.9 + 3.8Statistical test not reported. |
| Khateb et al. | 2005 | Switzerland | Single arm | **Target**Chronic cognitiveImpairment**Intervention**Donepezil**Frequency**3 months5 mg/day over 1 month and 10 mg/day over 2 months**Control**n/a | * Moderate to severe traumatic head injury for at least 6 months
 | * History of other previous central nervous system injury or disease
* Alcohol or drug abuse
* Severe speech or language disorders
* Unstable psychiatric disorders
* Compliance difficulties
* Current Acetylcholinesterase (AchE) inhibitors use
 | N = 10 Male – 6Female – 4Age – 43 (8)Ethnicity not reported | 100% moderate to severe TBI | Fatigue Questionnaire (29 items rated on a 7-point scale (‘do not agree at all’ to ‘agree completely’)and investigated fatigue severity, specificity, psychological consequences of fatigue and effects of sleep and/or rest on fatigue.) | Pre = 132.6 (27.3) post = 126.1 (32.3)Within group changes was not observed (Z=0.10, p=0.92) |
| Theadom et al. | 2018 | New Zealand | Randomized placebo-Controlled Trial | **Target** – Cognitive function after TBI**Intervention**Herbal supplement MLC901 (NeuroAiD IITM)**Frequency** 6 months2 capsules (0.4 g/capsule) TID**Control**Placebo | * Age 18-65;
* 1–12 months after mild or moderate TBI;
* Score >30 on the Cognitive Failures Questionnaire
 | * Coexisting injury or medical condition, which is severe or unstable, that could adversely impact outcome measures
* Severe TBI defined by GCS ≤8
* Current participation in another clinical trial
* Dependent on others for everyday activities before the onset of the brain injury
* Pregnant or breast feeding
* Not fluent in English or aphasia/dysphasia
* Known allergic any components of MLC901
* Unknown date of injury.
 | N = 78Male – 39Female – 39Ethnicity – New Zealand European - 49 Intervention group N = 36 Age – 38.58 (14.12)Control Group N = 42Age – 38.40 (15.74) | 100% TBI | Fatigue Impact Scale (FIS) | Intervention group: Baseline = 32.31 (19.47)1 month = 24(20.32)3 months = 22.50 (17.57)6months = 19.28 (17.65)9 months = 18.42 (16.5)Control group: Baseline = 34.48 (19.77) 1 month = 25.36 (19.96)3 months = 23.64 (18.03)6 months = 22.48 (19.02)9 months = 21.81 (19.11)No group significant differences were observed. |
| Table 1b. Psychological Intervention Summaries |
| **First author** | **Year** | **Country** | **Study Design** | **Intervention** | * **Inclusion**
 | * **Exclusion**
 | **Demographics** | **% TBI** | **Assessment** | **TBI specific FindingsStatistics** |
| Potter et al. | 2016 | UK | Two-center, randomized, open label, wait-list control | **Target**Persistent postconcussional symptoms**Intervention** CBT**Frequency**12 weekly 1-hour individual sessions**Control**Wait list | * Mild TBI within the last 6 months
* Postconcussion Disorder
 | * Non-fluent English,
* Mini-Mental State Exam <20 Or Frontal Assessment Battery <10,
* Barthel Index score <15,
* Previous receipt of 4+ sessionsof CBT after TBI,
* Other neurological disorder,
* Substance dependence,
* Risk of self-harm or severe psychiatric illness necessitating involvement of a Community Mental Health Team.
 | N = 46Male – 25Female – 21Age – 41.4 (1.6)Intervention groupN = 26Age – 40.1 +/- 10.3 Waiting list groupN = 20Age – 43.1 +/- 13.1Ethnicity not reported | Severe TBI – 20%Moderate TBI – 28%mild TBI – 52% | Checklist of IndividualStrength (CIS20R) | (Mean±SD (% above cut-off)CBT T1 = 98.2±19.5 (76%) CBT T2 = 86.8±25 (40%) Control T1 = 104.2±18 (75%) Control T2 = 100.8±26.3 (75%)CIS2OR was a significant covariate for T1-T2 (p=.025) |
| Lu et al. | 2016 | USA | Multiple case report | **Target**Insomnia, fatigue, pain, and mood symptoms**Intervention** CBT **Frequency**4 sessions of 60 minutes1 session per week**Control**n/a | * Adults with history of TBI
* Depression, anxiety, pain, or fatigue in addition to insomnia
 | * N/A
 | N = 3Case 1 – Asian, female, 60Case 2 – Caucasian, male 42Case – Caucasian, female, 59 | Case 1 mild TBICase 2 moderate TBICase 3 severe TBI | Multidimensional Assessment of Fatigue(MAF) | Case 1: 42 (pre), 33 (post), NA (follow-up) Case 2: 45 (pre), 43 (post), 40 (follow-up)Case 3: 5 (pre), 4 (post), NA (follow-up)Statistical comparisons were not included. |
| Nguyen et al. | 2017 | Australia | Parallel 2-group randomized controlled trial | **Target**Sleep disturbance and fatigue**Intervention** CBT **Frequency**6 modules addressing sleep and fatigue across 8 sessions**Control**Wait list / Treatment as usual (TAU) | * Age 16 to 65
* Mild to severe TBI
* Pittsburgh Sleep Quality Index score >5 and/or Fatigue Severity Scale score > 3
 | * Presence of other neurologic disorders,acute psychiatric symptoms substance abuse
* Trans meridian travel or night shift work in the 4 weeks preceding baselineassessmentSleep apnea
 | N = 24Male – 16Female – 8Age – 43.81 (12.95)CBT groupN = 13AGE – 45.53 (13.87)TAU groupN = 11Age – 41.90 (12.95)Ethnicity not reported | Severe TBI – 70.83%Moderate TBI – 8.33%Mild TBI – 20.83 | Fatigue Severity Scale (FSS) | CBT: 5.49 (0.17) [pre]; 5.41 (0.13) [post]; 5.34 (0.18) [end point]Wait-list control/TAU: 5.48 (0.20) [pre];5.21 (0.15) [post]; 4.95 (0.20) [end point]No significant interactions FSS |
| Brief Fatigue Inventory (BFI) | Significant interaction effect was observed on BFI and CBT condition (.82 points between groups (95% CI, 0.18-1.45; P<.05) post intervention, and after 4 months (1.54 (95% CI, 0.66-2.42;P<.01) |
| D’Antonio et al. | 2013 | USA | Randomized, active control | **Target** – major depressive disorder**Intervention** 1. Cognitive Behavioral Therapy (CBT)
2. Supportive Psychotherapy (SPT)

**Frequency**3 months treatment duration16 sessionstwice-weekly sessions for the first month and weekly sessions for months 2 and 3 First session 90 min, remaining sessions lasting 50 min.**Control**n/a | * 18 years or older
* History of TBI at least 12 months postinjury
* Meeting DSM-IV criteria for a major depressive episode not currently receiving psychological treatment and treatment-seeking during the course of participation.
 | * Prescribed mood medications and dosage not stable for at least 6 months,
* History of psychoticdisorder current substance abuse,
* Mental retardation
 | N = 44Male – 19Female – 25Age – 48.8 (10.2)CBT N = 22SPT N = 22Caucasian – 57%Hispanic – 20%African-American – 15% | 9% Mild TBI9.3% Moderate TBI14% - Severe TBI | Beck Depression Inventory (BDI) – Fatigue question | CBT: 1.41 (1.00) [pre]; 1.09 (0.91) [post]SPT: 1.50 (0.86) [pre]; 1.32 (0.99) [post]Neither group showed within group significant changes. |
| Leonard | 2002 | USA | Randomized controlled trial with two control conditions (education and waitlist control) | **Target****P**ostconcussion symptoms**Intervention** Group cognitive behavioral therapy (GCBT) sessionsGroup based education and support (GEST)**Frequency**Four sessions over four weeks of two hour each**Control**Wait list | * Age 18-65 years
* Mild TBI at least three months previously
* Meeting DSM-IV criteria for Postconcussion disorder
* Postconcussion syndrome as the primary psychiatric diagnosis
* Adequate intellectual capacity and verbal facility to participate in treatment.
 | * Previous CBT for Postconcussion symptoms
* Concurrent cognitive rehabilitation or CBT
* Other concurrent psychotherapy initiated within the month prior to the start of the study
* Ongoing, pre-morbid primary neurologic problems
* Significant medical problems that could interfere with treatment attendance or response
* Non-stabilized psychiatric medications
* history of psychotic disorder
* alcohol or substance dependence.
 | N = 40 GCBTN = 15Age – 39.07 (10.57)Male – 6Female – 9Caucasian – 14Hispanic – 1GESTN = 16Age – 38.88 (10.85)Male – 4Female – 12Caucasian - 12Hispanic – 4WaitlistN = 9Age – 45.56 (7.94)Male – 4Female – 5Caucasian – 8African-American – 1  | 100% mild TBI | General Health Survey Energy / Fatigue subscale | Mean (SD):GCBT – Pre = 39.33 (22.27)Post = 39.33 (23.59)GEST – Pre = 30.67 (16.13)Post = 37.33 (16.13)Waitlist –Pre = 43.33 (52.80)Post = 38.89 (21.03)Significant pre/post differences were not observed (p>.063). Fatigue specific group differences were not reported. |
| Ouellet et al. | 2004 | Canada | Case study | **Target**Insomnia**Intervention**CBT **Frequency**Eight weekly sessions**Control**n/a | * N/A
 | * N/a
 | N = 1 (male)Age – Late 30sEthnicity not reported | Moderate TBI – 100% | Multidimensional Fatigue Inventory (MFI) | Pre = 62Post = 52Follow-up = 64 (1 month)Follow-up = 52 (3 month)Statistics were not included in the abstract. |
| Raina et al. | 2016 | USA | Single blind randomized controlled trial, active control | **Target** fatigue**Intervention** Maximizing energy intervention for fatigue **Frequency**9 weeks – Two 30-minute 1:1 web-cam sessions per week over 8 week period**Control**Health Education | * Mild to severe TBI at least 6months postinjury
* Fatigue ≥4 on the Fatigue Severity Scale [FSS]
* Living within a 50-mile radius of the research site
* Adequate vision to use a computer
* Able to provide informed consent
* English-speaking
 | * FIM motor Score <65
* History of major depressive disorder
* Mania
* Hypomania
* Psychosis
* Substance abuse
* Non TBI disability
 | N = 38Male – 21Female – 17MAXN = 17Age – 43.8 (16.2)White – 17Health EducationN = 21Age – 48.1 (12.5)White – 18 | Severe TBI – 19Complicated Mild TBI – 15Moderate TBI – 4 | Modified Fatigue Impact Scale (FIS) | Change scores, mean (SD)MAX: FIS = -7.7 (13.6)Control:FIS = -0.2 (12.0)p =.092No significant group differences were observed |
| Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Scale | MAX:PROMIS = −4.7 (6.1) Control:PROMIS= −1.4 (7.1) p =.162No significant group differences were observed |
| Fatigue Severity Scale (FSS) | MAX:FSS = −1.3 (1.6)Control:FSS = −0.6 (1.0)p =.092 No significant group differences were observed |
| Howe et al. | 2019 | Norway | Single group pre/post | **Target**Post-concussive symptom management and cognitive**Intervention**Compensatory Cognitive Training (CCT)**Frequency**10 sessions2 hour/week**Control**n/a | * Age 18–60
* Residents of Oslo or Akershus county
* Mild-to-moderate TBI
* Employed in a minimum 50% position at the time of injury, and sick-listed 50% or more due to post-concussive symptoms
 | * Inability to speak or read Norwegian
* Severe preexisting neurological or psychiatric disorders
* Active substance abuse.
 | N = 6 Male – 3Female – 3Age – 40 (15)Ethnicity not reported | 100% mild – moderate TBI | Fatigue Severity Scale (FSS) only at baseline  | FSS median [IQR] Baseline = 5(2)3month data not provided |
| Rivermead Postconcussion Questionnaire (RPQ) -Fatigue | RPQBaseline = 2.53 months = 1Fatigue specific statistics were not included. |
| Liebenberg | 1997 | South Africa | Solomon 4 group design, active control (Treatment as usual (TAU)= 1 psycho-education session) . | **Target**Post-concussive symptom management.**Intervention**Educational session (TAU) + take-home psycho-education course in booklet and on tape with classical music on the background. **Frequency**Not specifiedTime-frame not specified**Control**Treatment as usual | * Age 18-35
* Glasgow Coma Scale between 13-15 at admission and 15 at discharge
* Galveston Orientation and Amnesia Test score of 70 at discharge
* Having a reliable and believable person at home who can monitor the behavior of the patient
* Speaking Afrikaans or English
* Have a cassette player
 | * preexisting head injury or psychiatric disorders
* more than 4 days of hospitalization
* less than 8 years of schooling
* Active substance abuse.
* have a skull fracture
 | N = 81 Male – 81Female – 0Age – not reportedWhite - 81 | 100% TBI (all 4 days post-injury) | Profile of Mood States Scale (POMS) – fatigue subscale | Mean (SD)Intervention group: Pre = 54.3 (12.0)Post = 49.3 (8.6)Control: Pre = 50.3 (10.8)Post = 44.1 (5.7)The author reports a significant reduction of fatigue in the Intervention group compared to the control group using Wilcoxon signed rank test.  |
| Table 1c. Exercise based intervention summaries |
| **First author** | **Year** | **Country** | **Study Design** | **Intervention** | * **Inclusion**
 | * **Exclusion**
 | **Demographics** | **% TBI** | **Assessment** | **TBI specific FindingsStatistics** |
| Kolakowsky-Hayner et al. | 2017 | USA | Prospective randomized single-blind crossover design  | **Target** Fatigue**Intervention** Walking**Frequency**Walking5% increase from baseline in first week and a goal reach 40% increase from baseline in 8 weekslast 4 weeks they should maintain that increase (40% from baseline) NutritionEquivalent frequency and intensity of contact with coaches who created individualized nutrition plans12 weeks**Control**Nutrition arm | * TBI within 6months that required medical attention
* Age 18+
* Ambulate unassisted (orthotic ok)
* English or Spanish speaking
* medically ok to participate (medical clearance).
 | * Participating in another PT program
 | N = 123; received interventionIntervention – 62Control – 61Male – 72Female – 51White – 79Black – 6Asian – 10Hispanic – 19Other - 9Age total – 42.7(15.5) | 100% TBI | Global Fatigue Index (GFI) | **GFI**Baseline: N = 114,24.3 (12.4)Mean difference post walking intervention: 5.1, p<0.001  |
| Barrow Neurological institute (BNI) | **BNI** (total)Baseline: N = 113,24.3 (18.3) Mean difference post walking intervention: 4.78, p<0.003  |
| Multidimensional Fatigue inventory (MFI) – General Fatigue | **MFI**Baseline: MFI-GF N = 114, 11.9 (4.1) Mean difference post walking intervention: -.75, p<0.05  |
| Chin et al. | 2015 | USA | Consecutive enrollees; no control | **Target**Cardiorespiratory Fitness**Intervention** vigorous aerobic exercise achieve 70-80% HR reserve**Frequency**30 minutes three days/ week 12 weeks **Control**n/a | * Nonpenetrating TBI >6 months prior to enrollment
* Nonsmokers
* Age 21-45 years
* Free of known metabolic, respiratory, or cardiovascular disease
* Able to walk independently on the treadmill without assistance or support
* Sedentary and not participating in any exercise programs
 | * Subjects participating in regular exercise of 3 or more times a week at intensities greater than 4 metabolic equivalents (METs)
* Pregnant at the time of enrollment
 | N = 10 completed the intervention Male – 4Female – 6Age:Subject 1 – 34Subject 2 – 32Subject 3 – 30Subject 4 – 35Subject 5 – 42Subject 6 – 29Subject 7 – 34Subject 8 – 23Subject 9 – 44Subject 10 – 26Ethnicity not reported | Mild TBI – 50%Moderate TBI – 40%Severe TBI – 10% | Fatigue Severity Scale (FSS) | FSS Composite scorePre = 4.1 (2.1) Post = 3.2 (1.9)*p* = 0.029 |
| Driver & Ede | 2009 | USA | Stratified randomized controlled design | **Target**Mood**Intervention** Physical activity aquatic program vs vocational rehab class**Frequency**3 session/week for 8 weeks**Control**No intervention | * TBI outpatients from study site’s rehabilitation center
* Rancho Los Amigos level above VI
* More than 1-year post TBI
 | * Rancho Los Amigos level 6 or less
 | N = 16Gender not reportedEthnicity not reportedIntervention group: Age – 38.78(2.45)Control group:Age – 37.62(1.78) | 100% TBI | POMS-fatigue | Intervention group Pre = 1.36+1.13Post = 0.5+0.58Control groupPre = 1.24+0.61Post = 1.29+0.57POMS fatigue item statistical comparison not reported. |
| Gemmell & Leathem | 2006 | New Zealand | Randomized wait-list control, within group design | **Target**General physical, social interaction and mental well-being **Intervention** Tai Chi**Frequency**45minute, twice weekly for 6 weeks **Control**Waitlist | * Sustained a mild, moderate, or severe TBI based on retrograde and/or anterograde amnesia
* Post-traumatic amnesia and/or loss of consciousness with associated outcomes.
 | * n/a
 | N = 18Male – N = 9Age – 51.2(8.7)Female – N = 9Age – 40.2(12.5)Ethnicity not reported | 100% TBI | Medical Outcome Scale Short Form 36 (MOS-SF-36) - Vitality | Intervention Pre = 47.14 (18.22)Post = 40.71 (22.25)ControlPre = 47.50 (20.18)Post = 38.75 (4.43)Between group t statisticPre: -.036Post: .245 |
| Table 1d. Complimentary Alternative Medicine-based intervention summaries |
| **First author** | **Year** | **Country** | **Study Design** | **Intervention** | * **Inclusion**
 | * **Exclusion**
 | **Demographics** | **% TBI** | **Assessment** | **TBI specific Findings Statistics** |
| Miller et al. | 2015 | USA | Multicenter, double blind, sham-controlled clinical trial. | **Target**Post-Concussion Symptoms**Intervention**Hyperbaric Oxygen (HBO)**Frequency**40 sessions at 1.5 atmospheres absolute (ATA)**Control**1. 40 sham sessions of room air at 1.2 ATA
2. no supplemental chamber procedures
 | * 18 y/o
* Still serving in the military
* TBI based hospital recruitment
* 1 or more lifetime mTBIs with persistent symptoms
* With 1 mTBI occurring during deployment to Operation Iraqi Freedom or during Freedom and the most recent at least 4 months before randomization
* Stable in medications for PTS or depressive symptoms. Assessment for claustrophobia.
 | * Lifetime h/o moderate to severe TBI
* Relative or absolute contraindications to HBO
* Current drug abuse.
 | Total N = 72Male – 69Female – 3Standard Care GroupN = 23Male – 23Female – 0Age – 30.3 (7.2) HBO GroupN = 24Male – 23Female – 1 Age – 32.5 (7.9) Sham GroupN = 25Male – 24Female – 0Age – 31.4 (7.6)Ethnicity not reported | 100% mild TBI | Short Form Health Survey (SF-36) vitality subscale | Mean change score Standard care group = −0.3 (20.6)HBO group = 7.2 (28.8) Sham group = 6.8 (18.9)Group comparison statistics not reported |
| Lagos et al. | 2013 | USA | Case study | **Target**Postconcussion Syndrome**Intervention**Hear Rate Variability Feedback (HRV).**Frequency**10 weeks of Heart Rate20-minute breathing practices each day**Control**n/a | * NA
 | * NA
 | Female – 1Ethnicity not reported | 100% concussion | Profile Mood States-Short Form - fatigue | At session 1 Fatigue score = 16 After session 10Fatigue score = 4 |
| Sinclair et al. | 2014 | Australia | Randomized placebo controlled | **Target** Fatigue**Intervention**Blue light therapy (BLT)**Frequency**4 weeks, 45 min/day based treatment with high intensity **Control**1. Yellow light therapy (YLT)

No treatment | * Age 18-65
* TBI at least 3 months earlier
* Self-reported significant fatigue (FSS ≥ 4) and/or sleep disturbances.
 | * Other medical illness accounting for fatigue
* Other neurological disorders
* Psychiatric illness requiring hospitalization
* Preinjury sleep disorders, or chronic fatigue syndrome
* Obesity or estimated high risk of Obstructive Sleep Apnea on the Berlin Questionnaire 28
* Trans meridian travel or night shift work in the preceding 6 weeks
* Current use of sleep medications
 | N = 30Age – 42.0 (13.6)Female – 6Male – 24Blue Light Therapy N = 10Male – 8Female – 2Age – 47.2 (13.7)Yellow Light Therapy N = 10Male – 9Female – 1Age – 36.2 (13.1)No Treatment Control N = 10Male – 7Female – 3Age – 42.5 (12.9)Ethnicity not reported | Severe TBI – 50%Moderate TBI – 27%Mild TBI – 23% | Fatigue Severity Scale (FSS) | BLT – 5.9 (0.8)YLT – 5.6 (05)No treatment control – 6.2 (0.4)Estimated coefficients of the Random Effects Regression analysisLinear regressionWeek = -0.04Week × Treatment groupBLT = -0.44YLT = -0.02Quadratic regressionWeek = 0.00Week × Treatment groupBLT = 0.04YLT = 0.00 |
| Qin | 2017 | Canada | Prospective case series | **Target**Sleep problems**Intervention**Hand Self Shiatsu (HSS)**Frequency**HSS protocol was taught and was required to be applied by participants before bedtime.Follow-up data collection occurred at 4 and 8 weeks**Control**Each participant acted as their own control | * Age 18-25
* Sports related concussion (SRC) diagnosis in the last 6 months
* Reported sleep disturbances after concussion
 | * Pre-existing self-reported sleep disturbance before developing a SRC
* Inability to communicate in English
* An active arthritic condition involving the hand or with unhealed hand injuries
* Noctambulism (sleepwalking)
* Sleep apnea
* Parasomnia
 | N = 14Male – 5 Female – 9Post-SRC GroupN = 7Male – 2Female – 5Age – 21.43 (2.15)Non-SRC GroupN = 7 Male – 3Female – 4Age - 22.57 (2.30)Ethnicity not reported | 100% - concussion | Flinders Fatigue Scale (FFS) | Post-SRC groupBaseline – 19.00(4.24)1st follow-up – 14.00(3.87)2nd follow-up – 13.29(4.79)Non-SRC groupBaseline – 15.14(6.12)1st follow-up – 14.00(4.87)2nd follow-up – 11.29(4.19)Friedman test, post-SRC group: X2(2)=6.46, p= .04non-SRC group: X2(2)=8.273, p= .02). |
| Baker & Wigram | 2004 | Australia | Volunteers recruited from rehabilitation unit | **Target**Mood **Intervention**Individual singing **Frequency**15 sessions three times week**Control**n/a | * 18-65 age
* TBI diagnosis
* < 12 months since PTA resolved
* No pre-trauma speech/ language disorder
 | * n/a
 | N = 4Age = 26.5 (2.08)Male 100%Ethnicity not reported | 100% TBI | Visual Analog Mood Scale | EnergeticLong term effects (sessions)*F*(3,104)= 1.84, *p* = 0.14Immediate effects (time)*F*(3,104) = 0.34, *p*= 0.79Cumulative effects (session x time)*F*(3,104)= 3.29, *p* < 0.05 TiredLong term effects (session)*F*(3,104)= 1.59*, p* = 0.20Immediate effects (time)*F*(3,104)= 0.04, *p*= 0.99Cumulative effects (session x time)*F*(3,104)= 0.47,*p*= 0.70 |
| Table 1e. Electrotherapy based intervention summaries |
| **First author** | **Year** | **Country** | **Study Design** | **Intervention** | * **Inclusion**
 | * **Exclusion**
 | **Demographics** | **% TBI** | **Assessment** | **TBI specific Findings Statistics** |
| Nelson & Esty | 2015 | USA | Case report | **Target**Traumatic Brain Injury/Post-Traumatic Stress Symptoms**Intervention**Electroencephalographic biofeedback**Frequency**25 sessions, 2-3 per week**Control**n/a | * n/a
 | * n/a
 | N = 2Sex not reportedAge not reportedEthnicity not reported | 100% TBI | Current Symptom Rating - Fatigue | Veteran 1Begin = 5.5End = 3.0Veteran 2Begin = 5.5End = 2.0 |
| Nelson & Esty | 2010 | USA | Case series | **Target**TBI Symptoms**Intervention**Electroencephalographic biofeedback **Frequency**3-38 sessions per participant; median 20 sessions**Control**n/a | * n/a
 | * n/a
 | N = 35Sex not reportedAge not reportedEthnicity not reported | 100% TBI | Visual analogue scale (VAS) symptom rating - Fatigue | Beta = -0.13R2 = 0.16F[1,296] = 57.49 |
| Smith et al. | 1994 | USA | Randomized double-blind study placebo control | **Target** Stress related symptoms of anxiety and depression**Intervention**Cranial electrotherapy stimulation (CES)**Frequency**45 mins daily, 4 days a week for 3 weeks**Control**Sham Placebo | * n/a
 | * n/a
 | N = 21 (11 controls, 10 treatment)Male – 21Female – 0Average age – 30100% Caucasian | 100%TBI | Profile of mood states | PretestPlacebo control = 8.17(7.41)Sham control = 9.46(7.83)CES = 7.44(6.75)Post testPlacebo control = 6.50(5.82)Sham control = 8.09(6.63)CES = 5.33(3.96)CES showed significant pre- post-intervention reduction in fatigue; no p-value reported |
| Table 1f. Multi-modal intervention summaries |
| **First author** | **Year** | **Country** | **Study Design** | **Intervention** | * **Inclusion**
 | * **Exclusion**
 | **Sample Size** | **% TBI** | **Assessment** | **Findings** |
| Rytter et al. | 2019 | Denmark | Stratified randomized controlled trial | **Target**Post-concussive symptoms**Intervention**Individual and group-based neuropsych treatment with exercise therapy and specialized, interdisciplinary, active rehabilitation programme (S-REHAB) physiotherapeutic coaching**Frequency**22week program**Control**Standard Care (STAND) | * Age 18-65
* At least 6mo post mTBI
* Persistent Post concussion symptoms of attention or memory +3 other PCS symptoms per ICD 10 within 4 weeks of injury continuing for at least 6 months
* Adequate Danish language skills
* Capable of attending sessions
* Able to participate in group therapy
* Own transport
 | * Other medical condition that prevent participation
* Pre-history of psychiatric disease
* Current psychiatric treatment
* Prehistory or current substance abuse
* Progressive neurologic disease
* Prehistory of moderate or severe TBI, chronic pain or migraine.
 | N = 89 used in analysis45 S-Rehab, and 44 standard care.Male – 30Female – 59STAND group :N = 44Male – 14Female – 30Age18–29 years – N =12 30–43 years – N = 2444<years – N =8 S-REHAB group:N = 45Male – 16Female – 29Age18–29 years – N = 1230–43 years – N = 2144<years – N =12 Ethnicity not reported | 100% Concussion | Multidimensional fatigue inventory (MFI-20) - Mental fatigue | Immediately post-treatmentMental fatigue STAND = 72.16 (17.23)S-REHAB = 65.11 (16.36)F = 5.72p = 0.019 |
| SF-36 - Energy/fatigue | STAND = 32.61 (19.72) S-REHAB = 37.67 (20.13)F = 3.27p = 0.074 |
| Multidimensional fatigue inventory (MFI-20) - Mental fatigue | 6-month follow-up Mental fatigue STAND = 69.89 (13.75)S-REHAB = 62.00 (19.32)F = 6.02p = 0.016 |
| SF-36 - Energy/fatigue | STAND = 36.25 (17.49) S-REHAB = 40.44 (21.10)F = 1.77p = 0.187 |
| Gagnon et al. | 2016 | Canada | Cohort design - pretreatment - post treatment  | **Target** Post-Concussion Symptoms**Intervention**Rehabilitation program for adolescents consisting of: - gradual monitored light aerobic exercise (60%),- coordination exercise,- mental imagery, reassurance, normalization of recovery, stress/anxiety reduction strategies**Frequency**2-15 weeks, mean 6.8 weeks (SD=4.7 weeks)**Control**n/a | * Age 14-18
* Diagnosis of sports concussion
 | * No coexisting cervical, oculomotor / vestibular impairments
 | N = 10Male -7 Female – 3Age :Case 1 – 16Case 2 – 16Case 3 – 15Case 4 – 17Case 5 – 16Case 6 – 16Case 7 – 18Case 8 – 14Case 9 – 17Case 10 – 18Ethnicity not reported | 100% Mild TBI | Post-concussion scale - Fatigue total score | Pre intervention = 52.1 ± 12.3Post intervention = 3.1 ± 9.1*t* = -5.91*p* = <0.001  |
| Gauvin-Lepage et al. | 2018 | Canada | Multicenter prospective quasi-experimental control group design | **Target**Post-concussion symptoms**Intervention**Aerobic activityCoordination/sport-specificActivityMental imageryEducationHome Program**Frequency**6 weeks**Control**Standard Care | * Age 8-17
* Concussion,
* French or English speaking
* Slow recovery 4 weeks after injury
* presenting with at least one PCS reported at least once a week
 | * Neck pain was the only PCS
* Sustained another concussion in the 6 months before the current injury
* Diagnoses preventing participation in the intervention or assessment of standing balance/ gait.
 | Intervention group N = 36Male – 15Female – 21Age – 14.0(1.9)Control group N = 13Male – 8Female – 5Age – 13.2(2.6)Ethnicity not reported | 100% Concussion | Post-Concussion Symptom Inventory (PCSI) | PCSIParentsControl – T1 = 4.62 (3.94)T2 = 3.69 (4.64)T3 = 1.42 (1.88)Exp - Pre (T1) = 3.58 (3.91)Post (T2) = 3.11 (3.46)T3 = 1.33 (2.96)ChildrenControl – T1 = 2.62 (2.39)T2 = 1.62 (1.44)T3 = 1.77 (3.00)Exp - T1 = 2.36 (2.24)T2 = 1.53 (1.81)T3 = 0.47 (1.29) |
| Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale – Total Fatigue Score | ParentsControl – T1 = 55.45 (12.57)T3 = 75.42 (15.69)Intervention - Pre (T1) = 62.98 (17.29)Post (T3) = 74.38 (16.55)ChildrenControl – T1 = 62.37 (26.63)T3 = 67.41 (19.89)Intervention - T1 = 59.89 (2.24)T3 = 73.80 (16.79) |

Abbreviations:

TBI: Traumatic brain Injury; GOS(E): Glasgow Outcome Scale (Extended); CNS: Centra Nervous System; GOS: Glasgow Outcome Scale; MMSE: Mini-Mental State Examination; BDI: Beck Depression Inventory; GCS: Glasgow Coma Scale; PSQI: Pittsburgh Sleep Quality Index; PTS: Pediatric trauma Score; EDS: Excessive Daytime Sleepiness; ECT: Electroconvulsive Therapy; CBT: Cognitive Behavioral Theory; SPT: Supportive Psychotherapy; GEST: Group -based Education and Support; MAX: Maximizing Energy; POMS: Profile of Mood States;GH: Growth Hormone; SRC: Sports-related Concussion; PCS; Post-concussion symptoms; FIM: Functional Independence Measure; LOC: Loss of Consciousness; PTA: Post Traumatic Amnesia; MFS: Mental Fatigue Scale; FSS: Fatigue Severity Scale; FIS: Fatigue Impact Scale; MAF: Multidimensional Assessment of Fatigue; BFI: Brief Fatigue Inventory; MFI: Multidimensional Fatigue Inventory; PROMIS: Patient-Reported Outcomes Measurement Information System; RPQ: Rivermead Postconcussion Questionnaire; GFI: Global Fatigue Index; BNI: Barrow Neurological institute; MFI: Multidimensional Fatigue inventory; MOS-SF-36: Medical Outcome Scale Short Form 36; SF-36: Short Form Health Survey; FFS: Flinders Fatigue Scale; PCSI: Post-Concussion Symptom Inventory; CES: Cranial Electrotherapy Stimulation; CIS20R: Checklist of Individual Strength; VAS: Visual Analogue Scale; PedsQL: Pediatric Quality of Life.