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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 mg  and week 4: 20 mg X 3.  **Control**  No Medication  Low 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 = 24  Male – 12  Female – 12  Age – 38.6 (11.1)  Ethnicity not reported | 100%  Mild TBI - 23  Moderate 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 Medication  Low 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 = 44  Male – 19  Female – 25  No medication group – 14  Low dose group – 15  Normal does group – 15  Age – 38.9 (10.8)  Ethnicity not reported | 100% mild TBI | Mental Fatigue Scale (MFS) | No Medication  21.7(6.3)  Low Dose =  18.3(5.6)  Normal Dose =  14.0 (4.8)  F=20.198, p<0.001  Significant 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 – 18  Age – 39.7 (12.5)  Ethnicity not reported | Moderate TBI – 4  Mild 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 = 36  Male – 27  Female – 9  Ethnicity –  Han – 22  Hui – 14  Intervention  N = 18  Age – 36.3 (10.9)  Placebo  N = 18  Age – 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 = 33  Melatonin N = 18  Placebo N = 15  Male – 22  Female – 11  Ethnicity not reported  Age – 37 (11) | Severe TBI – 28  Moderate TBI – 3  Mild TBI – 2 | Fatigue Severity Scale (FSS) | Adjusted means for sequence and period  Melatonin 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 = 39  Age – 1 – 18 years  Creatinine group  N = 20  Control  N = 19  Ethnicity 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 = 64  Male – 37  Female – 27  Ethnicity not reported  Control  N = 31  Age – 42.58 (14.64)  Treatment  N = 33  Age – 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 weeks  0.2 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 = 15  Male – 10  Female –5  Age – 45.5 (11.2)  Ethnicity – Caucasian -13  Hispanic – 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 weeks  100mg 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 = 51  Male – 35  Female – 16  Age – 38.25 (12.20)  Group A  N = 27  Group B  N = 24  Ethnicity –  White – 43  Hispanic – 5  Black – 2  Native 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 = 20  Male – 17  Female – 3  Placebo  N = 10  Age – 43 (19)  Modafinil  N = 10  Age – 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 = 13  Sex not reported  Ramelteon First N = 8  Age – 45.3 (19.7)  Placebo First  N = 5  Age – 38.2(14.8)  Total (N = 13)  Age – 42.5 (17.7)  Ethnicity not reported | Mild TBI – 7  Moderate to severe TBI – 6 | The Brunel Mood Scale: Fatigue | Intervention first:  Post = 8.6 +3.6  Placebo first:  Post = 9.2 + 4.5  Total= 8.9 + 3.8  Statistical test not reported. |
| Khateb et al. | 2005 | Switzerland | Single arm | **Target**  Chronic cognitive  Impairment  **Intervention**  Donepezil  **Frequency**  3 months  5 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 – 6  Female – 4  Age – 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 months  2 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 = 78  Male – 39  Female – 39  Ethnicity – New Zealand European - 49  Intervention group  N = 36  Age – 38.58 (14.12)  Control Group  N = 42  Age – 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 Findings Statistics** |
| 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+ sessions of 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 = 46  Male – 25  Female – 21  Age – 41.4 (1.6)  Intervention group  N = 26  Age – 40.1 +/- 10.3  Waiting list group  N = 20  Age – 43.1 +/- 13.1  Ethnicity not reported | Severe TBI – 20%  Moderate TBI – 28%  mild TBI – 52% | Checklist of Individual  Strength (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 minutes  1 session per week  **Control**  n/a | * Adults with history of TBI * Depression, anxiety, pain, or fatigue in addition to insomnia | * N/A | N = 3  Case 1 – Asian, female, 60  Case 2 – Caucasian, male 42  Case – Caucasian, female, 59 | Case 1 mild TBI  Case 2 moderate TBI  Case 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 baseline assessment Sleep apnea | N = 24  Male – 16  Female – 8  Age – 43.81 (12.95)  CBT group  N = 13  AGE – 45.53 (13.87)  TAU group  N = 11  Age – 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 duration  16 sessions  twice-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 psychotic disorder current substance abuse, * Mental retardation | N = 44  Male – 19  Female – 25  Age – 48.8 (10.2)  CBT N = 22  SPT N = 22  Caucasian – 57%  Hispanic – 20%  African-American – 15% | 9% Mild TBI  9.3% Moderate TBI  14% - 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) sessions  Group 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  GCBT  N = 15  Age – 39.07 (10.57)  Male – 6  Female – 9  Caucasian – 14  Hispanic – 1  GEST  N = 16  Age – 38.88 (10.85)  Male – 4  Female – 12  Caucasian - 12  Hispanic – 4  Waitlist  N = 9  Age – 45.56 (7.94)  Male – 4  Female – 5  Caucasian – 8  African-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 30s  Ethnicity not reported | Moderate TBI – 100% | Multidimensional Fatigue Inventory (MFI) | Pre = 62  Post = 52  Follow-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 = 38  Male – 21  Female – 17  MAX  N = 17  Age – 43.8 (16.2)  White – 17  Health Education  N = 21  Age – 48.1 (12.5)  White – 18 | Severe TBI – 19  Complicated Mild TBI – 15  Moderate TBI – 4 | Modified Fatigue Impact Scale (FIS) | Change scores, mean (SD) MAX:  FIS = -7.7 (13.6)  Control: FIS = -0.2 (12.0)  p =.092  No 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 =.162  No 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 sessions  2 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 – 3  Female – 3  Age – 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 | RPQ  Baseline = 2.5  3 months = 1  Fatigue 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 specified  Time-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 – 81  Female – 0  Age – not reported  White - 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 Findings Statistics** |
| Kolakowsky-Hayner et al. | 2017 | USA | Prospective randomized single-blind crossover design | **Target**  Fatigue  **Intervention**  Walking  **Frequency**  Walking  5% increase from baseline in first week and a goal reach 40% increase from baseline in 8 weeks  last 4 weeks they should maintain that increase (40% from baseline)  Nutrition  Equivalent frequency and intensity of contact with coaches who created individualized nutrition plans  12 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 intervention  Intervention – 62 Control – 61  Male – 72  Female – 51  White – 79  Black – 6  Asian – 10  Hispanic – 19  Other - 9  Age 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 – 4  Female – 6  Age:  Subject 1 – 34  Subject 2 – 32  Subject 3 – 30  Subject 4 – 35  Subject 5 – 42  Subject 6 – 29  Subject 7 – 34  Subject 8 – 23  Subject 9 – 44  Subject 10 – 26  Ethnicity not reported | Mild TBI – 50%  Moderate TBI – 40%  Severe TBI – 10% | Fatigue Severity Scale (FSS) | FSS Composite score  Pre = 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 = 16  Gender not reported  Ethnicity not reported  Intervention group:  Age – 38.78(2.45)  Control group:  Age – 37.62(1.78) | 100% TBI | POMS-fatigue | Intervention group  Pre = 1.36+1.13 Post = 0.5+0.58  Control group Pre = 1.24+0.61 Post = 1.29+0.57  POMS 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 = 18  Male – N = 9  Age – 51.2(8.7)  Female – N = 9  Age – 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)  Control Pre = 47.50 (20.18) Post = 38.75 (4.43)  Between group t statistic  Pre: -.036  Post: .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 = 72 Male – 69 Female – 3  Standard Care Group  N = 23  Male – 23  Female – 0  Age – 30.3 (7.2)  HBO Group  N = 24  Male – 23  Female – 1  Age – 32.5 (7.9)  Sham Group  N = 25  Male – 24  Female – 0  Age – 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 Rate 20-minute breathing practices each day  **Control**  n/a | * NA | * NA | Female – 1  Ethnicity not reported | 100% concussion | Profile Mood States-Short Form - fatigue | At session 1  Fatigue score = 16  After session 10  Fatigue 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 = 30  Age – 42.0 (13.6)  Female – 6  Male – 24  Blue Light Therapy  N = 10  Male – 8  Female – 2  Age – 47.2 (13.7)  Yellow Light Therapy  N = 10  Male – 9  Female – 1  Age – 36.2 (13.1)  No Treatment Control  N = 10  Male – 7  Female – 3  Age – 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 analysis  Linear regression  Week = -0.04  Week × Treatment group  BLT = -0.44  YLT = -0.02  Quadratic regression  Week = 0.00  Week × Treatment group  BLT = 0.04  YLT = 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 = 14  Male – 5  Female – 9  Post-SRC Group  N = 7  Male – 2  Female – 5  Age – 21.43 (2.15)  Non-SRC Group  N = 7  Male – 3  Female – 4  Age - 22.57 (2.30)  Ethnicity not reported | 100% - concussion | Flinders Fatigue Scale (FFS) | Post-SRC group  Baseline – 19.00(4.24)  1st follow-up – 14.00(3.87)  2nd follow-up – 13.29(4.79)  Non-SRC group  Baseline – 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= .04  non-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 = 4  Age = 26.5 (2.08)  Male 100%  Ethnicity not reported | 100% TBI | Visual Analog Mood Scale | Energetic  Long term effects (sessions)  *F*(3,104)= 1.84, *p* = 0.14  Immediate effects (time)  *F*(3,104) = 0.34, *p*= 0.79  Cumulative effects (session x time)  *F*(3,104)= 3.29, *p* < 0.05  Tired  Long term effects (session)  *F*(3,104)= 1.59*, p* = 0.20  Immediate effects (time)  *F*(3,104)= 0.04, *p*= 0.99  Cumulative 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 = 2  Sex not reported  Age not reported  Ethnicity not reported | 100% TBI | Current Symptom Rating - Fatigue | Veteran 1  Begin = 5.5  End = 3.0  Veteran 2  Begin = 5.5  End = 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 = 35  Sex not reported  Age not reported  Ethnicity not reported | 100% TBI | Visual analogue scale (VAS) symptom rating - Fatigue | Beta = -0.13  R2 = 0.16  F[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 – 21  Female – 0  Average age – 30  100% Caucasian | 100%  TBI | Profile of mood states | Pretest  Placebo control = 8.17(7.41)  Sham control = 9.46(7.83)  CES = 7.44(6.75)  Post test  Placebo 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 analysis 45 S-Rehab, and 44 standard care.  Male – 30  Female – 59  STAND group :  N = 44  Male – 14  Female – 30  Age  18–29 years – N =12  30–43 years – N = 24  44<years – N =8  S-REHAB group:  N = 45  Male – 16  Female – 29  Age  18–29 years – N = 12  30–43 years – N = 21  44<years – N =12  Ethnicity not reported | 100% Concussion | Multidimensional fatigue inventory (MFI-20) - Mental fatigue | Immediately post-treatment  Mental fatigue  STAND = 72.16 (17.23)  S-REHAB = 65.11 (16.36)  F = 5.72  p = 0.019 |
| SF-36 - Energy/fatigue | STAND = 32.61 (19.72)  S-REHAB = 37.67 (20.13)  F = 3.27  p = 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 = 6.02  p = 0.016 |
| SF-36 - Energy/fatigue | STAND = 36.25 (17.49)  S-REHAB = 40.44 (21.10)  F = 1.77  p = 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 = 10  Male -7  Female – 3  Age :  Case 1 – 16  Case 2 – 16  Case 3 – 15  Case 4 – 17  Case 5 – 16  Case 6 – 16  Case 7 – 18  Case 8 – 14  Case 9 – 17  Case 10 – 18  Ethnicity not reported | 100% Mild TBI | Post-concussion scale - Fatigue total score | Pre intervention = 52.1 ± 12.3  Post 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 activity  Coordination/sport-specific  Activity  Mental imagery  Education  Home 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 = 36  Male – 15  Female – 21  Age – 14.0(1.9)  Control group  N = 13  Male – 8  Female – 5  Age – 13.2(2.6)  Ethnicity not reported | 100% Concussion | Post-Concussion Symptom Inventory (PCSI) | PCSI  Parents  Control –  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)  Children  Control –  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 | Parents  Control –  T1 = 55.45 (12.57)  T3 = 75.42 (15.69)  Intervention -  Pre (T1) = 62.98 (17.29) Post (T3) = 74.38 (16.55)  Children  Control –  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.