

08.03.01 Cognitive Rehabilitation

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Related Policies:

- [08.03.04 Sensory Integration Therapy and Auditory Integration Therapy](#)

Summary

Description

Note: This evidence review is to only address the requests for outpatient cognitive rehabilitation.

Cognitive rehabilitation is a therapeutic approach designed to improve cognitive functioning after central nervous system insult. It includes an assembly of therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions. Cognitive rehabilitation comprises tasks to reinforce or reestablish previously learned patterns of behavior or to establish new compensatory mechanisms for impaired neurologic systems. Cognitive rehabilitation may be performed by a physician, psychologist, or a physical, occupational, or speech therapist.

Summary of Evidence

Post-Acute Sequelae of SARS-CoV-2 Infection

For individuals who have cognitive deficits due to post-acute sequelae of SARS-CoV-2 infection who receive cognitive rehabilitation delivered by a qualified professional, no relevant evidence was identified. Relevant outcomes are functional outcomes and quality of life. Systematic reviews have reported on the prevalence and duration of cognitive symptoms among individuals with varying acute infection severity and treatment settings. Limited reports examining the outcomes of rehabilitation in individuals with post-acute COVID-19 have primarily focused on physical and respiratory rehabilitation. Additionally, the natural history of cognitive deficits experienced by individuals who have recovered from acute COVID-19 requires further elucidation. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Dementia

For individuals who have cognitive deficits due to dementia who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, case series, and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Cochrane systematic review focusing on outcomes related to everyday function found statistically significantly improved participant self-ratings of goal attainment related to everyday functioning both immediately following rehabilitation and after 3 to 12 months follow-up post-rehabilitation. There was less certainty regarding whether cognitive rehabilitation had a meaningful effect on quality of life. One large RCT evaluating a goal-oriented cognitive rehabilitation program reported a significantly less functional decline in 1 of 2 functional scales and lower rates of institutionalization in the cognitive rehabilitation group compared with usual care at 24 months. These results need replication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Multiple Sclerosis (MS)

For individuals who have cognitive deficits due to MS who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Systematic reviews of RCTs have shown no significant effects of cognitive rehabilitation on cognitive outcomes. Although numerous RCTs have investigated cognitive rehabilitation for MS, high-quality trials are lacking. The ability to draw conclusions based on the overall body of evidence is limited by the heterogeneity of samples, interventions, and outcome measures. Further, results of the RCTs evaluated are mixed, with positive studies mostly reporting short-term benefits. Evidence for clinically significant, durable improvements in cognition is currently lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Stroke

For individuals who have cognitive deficits due to stroke who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Four systematic reviews evaluating 3 separate domains of cognitive function have shown limited effects of cognitive rehabilitation or effects of clinical importance. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Traumatic Brain Injury (TBI)

For individuals who have cognitive deficits due to TBI who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, case series, and systematic reviews. Relevant outcomes are functional outcomes and quality of life. The cognitive rehabilitation trials have methodologic limitations and have reported mixed results, some RCTs have shown improvements in some outcomes with cognitive rehabilitation in individuals with moderate-severe TBI, systematic reviews have provided mixed findings with no consistent evidence of efficacy in patients with TBI. Systematic reviews have generally concluded that efficacy of cognitive rehabilitation is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes, however, even though there is a paucity in the peer-reviewed scientific evidence in showing consistent evidence regarding the effectiveness of cognitive rehabilitation for cognitive deficits due to TBI, for certain carefully-selected individuals this treatment is widely considered to be in accordance with generally accepted standards of medical practice in the United States and will be considered medically necessary when the criteria below are met, see [Policy](#).

Miscellaneous Indications

For individuals who have cognitive deficits due to post encephalopathy, autism spectrum disorder (ASD), epilepsy, coma, brain tumor(s) or previous treatment of cancer, and cancer, who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, and case series. Relevant outcomes are functional outcomes and quality of life. The quantity of studies for these conditions is much less than that for the other cognitive rehabilitation indications. Systematic reviews generally have not supported the efficacy of cognitive rehabilitation for these conditions. Relevant RCTs have had methodologic limitations, most often very short lengths of follow-up, which do not permit strong conclusions about efficacy. Outpatient cognitive rehabilitation is insufficient to permit conclusions. Larger studies with longer follow up are needed to demonstrate durable benefits of cognitive rehabilitation therapy in these individuals. The evidence is not sufficient to draw conclusions on effect on health outcomes.

Additional Information

Clinical input obtained in 2010 provided the strongest support for the use of cognitive rehabilitation as part of the treatment of traumatic brain injuries. As part of clinical input obtained in 2015, the American Association of Physical Medicine & Rehabilitation reasserted its position of support. Cognitive rehabilitation may be considered medically necessary for traumatic brain injury based on this input.

OBJECTIVE

The objective of this evidence review is to determine whether cognitive rehabilitation delivered by a qualified professional improves the net health outcome in individuals with cognitive deficits.

PRIOR APPROVAL

Not applicable.

POLICY

Note: This evidence review is to only address the requests for outpatient cognitive rehabilitation.

Medically Necessary

Cognitive rehabilitation may be considered **medically necessary** in the rehabilitation of individuals with a cognitive impairment due to traumatic brain injury (TBI) referring to the disruption of normal brain functioning due to, but not limited to, **one of** the following:

- Concussion; **and/or**
- Traumatic cerebral edema; **and/or**
- Diffuse or focal traumatic brain injury including contusion or traumatic intra-axial hemorrhage of the cerebrum, cerebellum, or brainstem; **and/or**
- Traumatic extra-axial hemorrhage in the epidural, subdural or subarachnoid spaces

And all of the following criteria must be met:

- Therapy must be prescribed by the attending physician as part of the written care plan; **and**
- The service(s) must be provided by a qualified licensed professional (i.e., physician, a psychologist, physical therapist, occupational therapist and/or speech therapist); **and**
- The individual should have the potential for improvement (based on preinjury function); **and**
- Individuals must be able to participate actively in the program. (Active participation requires sufficient cognitive function to understand and participate in the program, as well as adequate language expression and comprehension i.e., participants should not have severe aphasia); **and**
- If ongoing services are requested, documentation should demonstrate continued objective improvement in function as identified in short - and long-term goals.

Investigational

Cognitive rehabilitation is considered **investigational** for all other indications (except for traumatic brain injury) including but not limited to the following because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes:

- Aging population
- Autism spectrum disorder (ASD)
- Cancer including but not limited to:
 - Brain tumor(s)
 - Pediatric cancer
 - Cancer survivors/previous treatment for cancer
- Coma Stimulation/Coma Arousal Program/Therapy
- Post-Acute Cognitive Sequelae of SARS-CoV-2 Infection
- Dementia
- Epilepsy/Seizure Disorder
- Maintenance therapy/preventative intervention (See [Policy Guidelines](#))
- Multiple Sclerosis (MS)
- Post-encephalopathy
- Stroke
- When the above criteria is not met

POLICY GUIDELINES

- Cognitive rehabilitation may be performed by an occupational therapist, physical therapist, speech/language pathologist, neuropsychologist or other psychologist, or a neuropsychiatrist, psychiatrist, or other physician.
- Cognitive rehabilitation must be distinguished from occupational therapy; occupational therapy describes rehabilitation that is directed at specific environments (i.e., home or work). In contrast, cognitive rehabilitation consists of tasks designed to develop the memory, language, and reasoning skills that can then be applied to specific environments.

- Services will be counted toward any applicable therapy visit limits in the individual subscriber contract when cognitive rehabilitation is performed by a physical, occupational and/or speech therapist as part of an outpatient rehabilitation/therapy program for individuals who have suffered a traumatic brain injury.

Dementia

Dementia is considered to be a group of conditions characterized by brain function impairments such as judgment and memory loss (e.g., Alzheimer's Disease).

Maintenance Therapy

A maintenance therapy program includes activities that maintain the individual's present level of function and prevent regression of that function. Maintenance begins when the therapeutic goals of a treatment plan have been achieved or when no further functional progress is apparent or expected to occur. For services to be considered medically necessary, there must be a potential for improvement (based on preinjury function). Ongoing services are considered necessary only when there is demonstrated continued objective improvement in function.

Cognitive Rehabilitation Treatment Duration

Duration and intensity of cognitive rehabilitation therapy programs vary. One approach for comprehensive cognitive rehabilitation is a 16-week outpatient program consisting of 5 hours of therapy a day, 4 days per week. In another approach, cognitive group treatment occurs for three 2-hour sessions each week and three 1-hour session (total of 9 hours per week). Cognitive rehabilitation programs for specific deficits (e.g. memory training) deficits which may be considered less intensive, generally have 1 or 2 sessions (30 to 60 minutes) per week for 4 to 10 weeks.

Coding

See the [Codes](#) table for details.

BACKGROUND

Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual's ability to think, use judgment, and make decisions. The focus is on improving deficits in memory, attention, perception, learning, planning, and judgment. The term cognitive rehabilitation is applied to various intervention strategies or techniques that attempt to help patients reduce, manage, or cope with cognitive deficits caused by brain injury. The desired outcomes are improved quality of life and function in home and community life. The term rehabilitation broadly encompasses reentry into familial, social, educational, and working environments, the reduction of dependence on assistive devices or services, and general enrichment of quality of life. Individuals recuperating from traumatic brain injury have traditionally been treated with some combination of physical therapy, occupational therapy, and psychological services as indicated. Cognitive rehabilitation is considered a separate service from other rehabilitative therapies, with its own specific procedures.

According to the American Association of Neurological Surgeons (AANS) in 2020, a traumatic brain injury (TBI) is a disruption in the normal function of the brain that can be caused by a blow, bump or jolt to the head, the head suddenly and violently hitting an object or when an object pierces the skull and enters brain tissue.

Observing one of the following clinical signs constitutes alteration in the normal brain function:

- Loss of or decreased consciousness.

- Loss of memory for events before or after the event (amnesia).
- Focal neurological deficits such as muscle weakness, loss of vision, change in speech.
- Alteration in mental state such as disorientation, slow thinking or difficulty concentrating.

Note: A maintenance program consists of activities that preserve the individual's present level of function and prevents regression of that function. Maintenance begins when the therapeutic goals of a treatment plan have been achieved, or when no additional functional progress is apparent or expected to occur.

Regulatory Status

Cognitive rehabilitation is not subject to regulation by the U.S. Food and Drug Administration (FDA).

RATIONALE

This evidence review was created in June 2003 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This review evaluates evidence for cognitive rehabilitation delivered by a qualified professional. Studies of self-administered computer programs are not considered cognitive rehabilitation for this evidence review and are not assessed here. Short-term improvements in cognitive test performance measured post-intervention alone will not be considered a health outcome for this review. Measurements of daily functioning and quality of life are the primary health outcomes of interest. Improvements should be demonstrable after longer-term follow-up post-intervention, preferably greater than 6 months.

Traumatic Brain Injury

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation, in individuals with cognitive deficits due to TBI.

The question addressed in this evidence review is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to TBI?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to TBI. The severity of TBI is commonly objectively assessed using the Glasgow Coma Scale (GCS) based on impairment of conscious level. The GCS measures 3 components - levels of eye, verbal, and motor responsiveness. GCS scores can range from 3 (lowest level of responsiveness) to 15 (highest level of responsiveness). Based on associations between GCS score and outcomes, TBI severity has been classified as Mild=GCS of 13 to 15, Moderate=GCS of 9 to 12, and Severe=GCS of 3 to 8.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after central nervous system (CNS) insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without a specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to TBI has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, a minimum of 6 months of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Austin et al (2024) reported results of a systematic review and meta-analysis of cognitive rehabilitation interventions in veterans and service members with traumatic brain injuries. The review included RCTs published by February of 2023 that used adult participants who were US veterans or active-duty service members who had a history of mild-to-moderate TBI that tested cognitive rehabilitation treatments designed to improve cognition and/or everyday functioning and reported objective neuropsychological testing as a primary outcome measure. 8 trials (N = 303 in cognitive rehabilitation; N=261 in control; 97% of whom had a history of mild TBI) were included. 7 of the 8 trials were published after 2013. The mean

age of participants was 37 years (SD=7) and between 81% and 100% of participants were male. Limited racial and ethnic information was available from the included studies. The mean length of time since TBI was 6 years (SD=52). Cognitive rehabilitation intervention lengths ranged from 4 to 15 weeks (mean=9.5; SD=). Study quality and risk of bias were evaluated using the Cochrane tool. Overall, the studies were rated as having low risk of bias. Given the variation in outcome measures used across studies, effect sizes were transformed into Cohen's d for meta-analysis. Participants in cognitive rehabilitation showed a significant improvement in overall objective neuropsychological functioning compared to controls (d = 0.22; 95% CI, 0.01 to 0.43; p=.04) but not on performance-based measures of functional capacity (d = 0.16; 95% CI, -0.48 to 0.81; p=.62). Participants in cognitive rehabilitation also had comparatively larger improvements in memory (d= 0.42; 95% CI, 0.13 to 0.70; p=.01) and executive functioning (d = 0.26; 95% CI, 0.01 to 0.51; p=.04) but not on attention (d=0.12; 95% CI, -0.12 to 0.35; p=.33). 4 of the RCTs included postintervention follow-up visits to measure durability of treatment effects. In these 4 studies, treatment effects on overall neuropsychological test performance at 10- or 12-week follow-up were also statistically significant favoring cognitive rehabilitation (d = 0.45; 95% CI, 0.01 to 0.90; p=.04).

A 2013 Cochrane review assessed cognitive rehabilitation for executive dysfunction (planning, initiation, organization, inhibition, problem-solving, self-monitoring, error correction) in adults with nonprogressive acquired brain damage. Sixteen RCTs (N=660 patients; 395 TBI, 234 stroke, 31 other acquired brain injury) were included in pooled analyses. No statistically significant effects on measures of global executive function or individual component functions were found.

A 2008 TEC Assessment evaluated cognitive rehabilitation specifically for adults with TBI. The objective of this Assessment was to determine whether the evidence showed that cognitive rehabilitation improved health outcomes. Eleven RCTs for specific cognitive deficits showed inconsistent support for cognitive rehabilitation. Of these 11 studies, 8 reported daily functioning or quality of life outcomes. Three studies showed statistically significant differences between intervention groups and control groups on 1 outcome. However, 2 studies were extremely small. Findings were inconsistent across other outcomes measured. In 1 study, significant findings after the intervention were no longer present at 6-month follow-up. All 11 trials also reported outcomes of various cognitive tests. These trials had numerous methodologic limitations, such as small sample sizes, lack of long-term follow-up, minimal interventions, and multiple outcomes. In summary, the RCTs considered in this Assessment did not show strong evidence for efficacy in the treatment of TBI.

Randomized Controlled Trials

Numerous RCTs have been conducted and are summarized in the systematic reviews described in the previous section.

Chiaravalloti et al (2016) conducted an RCT evaluating the Story Memory Technique to improve learning and memory in subjects with moderate-severe TBI. Sixty-nine subjects were randomized to treatment or control. Assessments were performed at the end of treatment (5 weeks) and 6 months posttreatment. Statistically significant outcomes favored the treatment group for several measures assessing memory at 5 weeks, while results at 6 months were less definitive.

das Nair et al (2019) conducted the large (N=328), multicenter, assessor blinded, RCT, which evaluated a group memory rehabilitation program for people with TBI (ReMemBrIn) in 9 sites in England. The group memory rehabilitation intervention involved 10 weekly sessions, each lasting about 1.5 hours, which were delivered by a trained Assistant Psychologist to groups of between 4 to 6 participants. The intervention focused on retraining memory functions and strategies to improve encoding and retrieval. The control group received usual care, which typically included employment rehabilitation services, self-help groups, or specialist charity support. Between 2013 and 2015, 328 individuals were randomized to therapy

(N=171) or usual care (N=157). The participants were characterized by a mean age of 45.1 years, median GCS closest to admission of 11.5 (25th, 75th centile=6, 14), a length of initial hospital stay for TBI of 84.2 days, and time since TBI of 100.9 months. On the primary outcome of frequency of memory failures in daily life assessed using the Everyday Memory Questionnaire-patient version at 6 months' follow-up, the between-group difference was not clinically important (adjusted difference in mean scores – 2.1 ; 95% confidence interval [CI] –6.7 to 2.5; p=.37). For secondary outcomes, there was a significant improvement in goal attainment both at 6 and 12 months, but no differences on others such as mood or quality of life. Important methodological limitations included lack of an active control arm, incomplete assessment of intervention fidelity, and exclusion of over 20% of the sample from the primary analysis.

Section Summary: Traumatic Brain Injury

Although some RCTs have shown improvements in some outcomes with cognitive rehabilitation in individuals with moderate-severe TBI, systematic reviews have provided mixed findings. In a systematic review of RCTs conducted from 2013 to 2023 including US Veterans with mild to moderate TBI, participants receiving cognitive rehabilitation showed a significant improvement in overall neuropsychological functioning, memory, and executive functioning but not in functional capacity or attention compared to controls. The benefits were durable for at least 3 months.

Dementia

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional in individuals with cognitive deficits due to dementia is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to dementia. This includes patients with AD.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to dementia has varying lengths of follow-up, ranging from 3 months to 2 years. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Kudlicka et al (2023) reported results of a Cochrane systematic review of cognitive rehabilitation for people with mild to moderate dementia on outcomes related to everyday functioning. The review included 6 trials (N=1702) published between 2010 and 2022. The mean age of participants in the RCTs ranged from 76 to 80 years and the proportion of male participants ranged from 29% to 79%. Approximately 60% participants had a diagnosis of AD. Risk of bias was rated as relatively low for all domains other than blinding, which is not generally feasible with psychosocial interventions. Extracting data for the outcome of everyday functioning was operationalized by extracting the measure of goal attainment used in the individual studies related to activities targeted in the intervention for that study. Results were provided for outcomes at the end of the cognitive rehabilitation and after 3 to 12 months of follow-up post-rehabilitation. The authors concluded that there was high-certainty evidence of large positive effects of cognitive rehabilitation relative to control immediately following rehabilitation on participant self-ratings of goal attainment (standardized mean difference (SMD)=1.5; 95% CI, 1.3 to 1.7; 3 RCTs; N=501), informant ratings of goal attainment (SMD=1.6; 95% CI, 1.01 to 2.21; 3 RCTs; N=476), and self-ratings of satisfaction with goal attainment (SMD=1.3; 95% CI, 1.1 to 1.5; 3 RCTs; N=501). The authors also concluded that there was high-certainty evidence showing a large positive effect of cognitive rehabilitation after 3 to 12 months of follow-up post-rehabilitation on participant self-ratings of goal attainment (SMD=1.5; 95% CI, 1.3 to 1.7; 2 RCTs, N=432), informant ratings of goal attainment (SMD=1.3; 95% CI, 0.78 to 1.72; 3 RCTs; N=446), and self-ratings of satisfaction with goal attainment (SMD=1.2; 95% CI, 0.7 to 1.7; 2 RCTs; N=432). There was less certainty regarding whether cognitive rehabilitation had a meaningful effect on other outcomes immediately or after 3 to 12 months such as participant anxiety and quality of life.

In a Cochrane review, Bahar-Fuchs et al. (2019) evaluated the use of cognitive training for people with mild to moderate dementia. They searched ALOIS, the Cochrane Dementia and Cognitive Improvement They 33 included trials were published between 1988 and 2018 and were conducted in 12 countries; most were unregistered, parallel-group, single-site RCTs, with samples ranging from 12 to 653 participants. Interventions were between two and 104 weeks long. We classified most experimental interventions as 'straight CT', but we classified some as 'augmented CT', and about two-thirds as multi-domain interventions. Researchers investigated 18 passive and 13 active control conditions, along with 15 alternative treatment conditions, including occupational therapy, mindfulness, reminiscence therapy, and others. The methodological quality of studies varied, but we rated nearly all studies as having high or unclear risk of selection bias due to lack of allocation concealment, and high or unclear risk of performance bias due to lack of blinding of participants and personnel. We used data from 32 studies in the meta-analysis of at least one outcome. Relative to a control condition, we found moderate-quality evidence showing a small to moderate effect of CT on our first primary outcome, composite measure of global cognition at end of treatment (standardized mean difference (SMD) 0.42, 95% confidence interval

(CI) 0.23 to 0.62), and high-quality evidence showing a moderate effect on the secondary outcome of verbal semantic fluency (SMD 0.52, 95% CI 0.23 to 0.81) at end of treatment, with these gains retained in the medium term (3 to 12 months post treatment). In relation to many other outcomes, including our second primary outcome of clinical disease severity in the medium term, the quality of evidence was very low, so we were unable to determine whether CT was associated with any meaningful gains. When compared with an alternative treatment, we found that CT may have little to no effect on our first primary outcome of global cognition at end of treatment (SMD 0.21, 95% CI -0.23 to 0.64), but the quality of evidence was low. No evidence was available to assess our second primary outcome of clinical disease severity in the medium term. We found moderate-quality evidence showing that CT was associated with improved mood of the caregiver at end of treatment, but this was based on a single trial. The quality of evidence in relation to many other outcomes at end of treatment and in the medium term was too low for us to determine whether CT was associated with any gains, but we are moderately confident that CT did not lead to any gains in mood, behavioral and psychological symptoms, or capacity to perform activities of daily living. Limitations were noted as the quality of the studies we reviewed varied but overall was not very high, so the certainty in some of these findings is low. Future studies should continue improving on quality, should continue comparing CT with other treatments, and should follow participants for a longer period to understand whether observed benefits for cognition last beyond the short or medium term. The authors concluded relative to a control intervention, but not to a variety of alternative treatments, CT is probably associated with small to moderate positive effects on global cognition and verbal semantic fluency at end of treatment, and these benefits appear to be maintained in the medium term. Our certainty in relation to many of these findings is low or very low. Future studies should take stronger measures to mitigate well-established risks of bias and should provide long-term follow-up to improve our understanding of the extent to which observed gains are retained. Future trials should also focus on direct comparison of CT versus alternative treatments rather than passive or active control conditions.

Huntley et al. (2015) performed a meta-analysis of cognitive interventions in dementia. Thirty-three studies were included. Interventions were divided into categories such as cognitive training, cognitive stimulation, and cognitive rehabilitation. Studies classified as cognitive stimulation had a significant effect as measured on the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale. Reviewers concluded that benefits measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale were generally not clinically significant.

In a Cochrane review, Bahar-Fuchs et al. (2013) evaluated the use of cognitive training (task-focused) or rehabilitation (strategy-focused) in AD and vascular dementia. Evidence from 11 RCTs did not demonstrate improved cognitive function, mood, or activities of daily living in patients with mild-to-moderate AD or vascular dementia with cognitive training. Reviewers cited a 2010 high-quality RCT of cognitive rehabilitation in 69 patients with early-stage AD, which showed short-term improvements in patient-rated outcomes. A 2011 Cochrane review assessing interventions for persons with mild cognitive impairment concluded that there was little evidence on the effectiveness or specificity of such interventions because improvements observed were similar to effects seen with active control interventions.

Randomized Controlled Trials

Individual randomized trials not included in the systematic reviews have shown variable outcomes of cognitive rehabilitation; see the tables below.

Clare et al. (2019) completed a randomized controlled trial to determine whether individual goal-oriented cognitive rehabilitation (CR) improves everyday functioning for people with mild-to-moderate dementia. Parallel group multicenter single-blind randomized controlled trial (RCT) comparing CR added to usual treatment (CR) with usual treatment alone (TAU) for people with an ICD-10 diagnosis of Alzheimer,

vascular or mixed dementia, and mild-to-moderate cognitive impairment (Mini-Mental State Examination [MMSE] score ≥ 18), and with a family member willing to contribute. Participants allocated to CR received 10 weekly sessions over 3 months and four maintenance sessions over 6 months. Participants were followed up 3- and 9-months post randomization by blinded researchers. The primary outcome was self-reported goal attainment at 3 months. Secondary outcomes at 3 and 9 months included informant-reported goal attainment, quality of life, mood, self-efficacy, and cognition and study partner stress and quality of life. The results randomized (1:1) 475 people with dementia; 445 (CR = 281) were included in the intention to treat analysis at 3 months and 426 (CR = 208) at 9 months. At 3 months, there were statistically significant large positive effects for participant-rated goal attainment ($d = 0.97$; 95% CI, 0.75-1.19), corroborated by informant ratings ($d = 1.11$; 95% CI, 0.89-1.34). These effects were maintained at 9 months for both participant ($d = 0.94$; 95% CI, 0.71-1.17) and informant ($d = 0.96$; 95% CI, 0.73-1.2) ratings. The observed gains related to goals directly targeted in the therapy. There were no significant differences in secondary outcomes. The authors concluded CR enables people with early-stage dementia to improve their everyday functioning in relation to individual goals targeted in the therapy. Limitations were noted and should be considered. Due to the constraints of trial design, the goal-setting interview was conducted by researchers not involved in delivering therapy, whereas in clinical practice, the goal-setting process would be undertaken by the therapist and might be more efficient. While participants were invited to select up to three goals, on average, the therapists were able to address two goals per participant. The primary outcome was based on ratings of progress with all goals identified at baseline, rather than just those goals that were actually addressed; therefore, the overall estimate of improvement in goal attainment is a conservative one. Ratings for the goals that were directly addressed showed a clinically meaningful degree of change. The trial design did not allow us to conclusively demonstrate that benefits were due to the specific effects of CR rather than nonspecific effects of contact with a therapist; however, the observed gains related specifically to improvements in functional ability for goals directly targeted in the therapy, and in the pilot trial, CR demonstrated benefits over an active control condition. In selecting secondary outcome measures, it would have been useful to include a measure of functional ability.

Regan et al. (2017) reported on an RCT of a home-based, 4-session, goal-oriented cognitive rehabilitation program versus usual care in 55 patients with mild cognitive impairment and early AD. Patients were community-dwelling with a diagnosis of mild cognitive impairment or AD within 6 months of enrollment and an MMSE score greater than 20. The intervention group received 4 weekly 1-hour therapy sessions delivered by experienced therapists with a focus on addressing personally meaningful goals. All participants identified at least one goal for improvement. The usual care group had no contact with the research team between their initial and final assessments. The primary outcome measures were goal performance and satisfaction scores on the Canadian Occupational Performance Measure. Twelve participants in the intervention group and three participants in the control group discontinued study participation and were excluded from the final, per-protocol analysis. For the first identified goal, the intervention group had significantly greater improvements in performance and satisfaction on the Canadian Occupational Performance Measure than the control group. There were no differences in secondary measures of quality of life or anxiety and depression. The per-protocol results were biased due to the high rate of missing data.

Ameiva et al. (2016) reported on results from the group and individual cognitive therapies in Alzheimer's disease (ETNA3) multicenter RCT that compared 4 therapies strategies: standardized programs of cognitive training (group sessions), reminiscence therapy (group sessions), individualized cognitive rehabilitation program (individual sessions), and usual care. Six hundred fifty-three patients with mild-to-moderate AD were randomized in a 1:1:1:1 ratio at 40 French clinical sites. We focus on the cognitive rehabilitation program and usual care arms. The primary outcome was the rate of survival without moderately severe to severe dementia at 2 years. Secondary outcomes were cognitive impairment, functional disability, behavioral disturbance, apathy, quality of life, depression, caregiver burden, and

resource utilization. Participants and clinical staff were not blinded to treatment assignment, but outcome assessments were done by blinded physicians and psychologists. The cognitive rehabilitation therapy consisted of a “made-to-measure” program conducted in individual sessions and adapted to patients’ cognitive abilities, with goals selected to be personally relevant to the patient. Intention-to-treat analyses were performed using “missing equal failure” to replace missing values. Approximately 90% of participants had a 3-month follow-up visit, and 72% had a 24-month visit. There was no difference between the cognitive rehabilitation group and the usual care group with respect to the primary outcome. However, patients who received cognitive rehabilitation therapy had a less functional decline at 24 months compared with the usual care group, as measured by 1 of the 2 scales assessing functional abilities: the Autonomie Gérontologique Groupes Iso-Ressources scale ($p=.02$). The rate of institutionalization was lower in the cognitive rehabilitation therapy group (27%) than in the usual care group (19%). These results are promising but given the lack of consistency in benefits on the 2 functional scales, replication is needed to confirm these positive findings.

Thivierge et al. (2014) in Canada reported on a small ($N=20$), assessor-blinded, block-randomized, crossover trial of an individualized memory rehabilitation program in patients with mild-to-moderate AD. The Memory Rehabilitation Program comprised 4 weeks of training by a patient's caregiver to improve performance of an instrumental activity of daily living selected by the patient and caregiver. Errorless learning (assistance provided to minimize errors) and spaced retrieval (expanded delays, from 30 seconds to 8 minutes, between each correct performance of the task) were used to facilitate learning at each patient's own pace. The primary outcome was a measure of assistance required to perform the task correctly at 1, 4, and 8 weeks after training. Compared with untrained (in period 1) or previously trained (in period 2) controls, statistically, significant improvements in performance were observed at posttreatment week 1 in both periods and at posttreatment week 4 in period 2. A statistically significant improvement in performance occurred in period 1 controls compared to baseline. Performance of the target instrumental activity of daily living declined within 2 to 3 months post-training. Improvements in other outcomes (general memory and cognitive ability, overall function, quality of life, and behavioral/psychological symptoms) were not observed.²¹,

Kurz et al. (2012) conducted an RCT of patients with AD and early dementia. The population was comprised of 201 patients with clinical evidence of dementia and an MMSE score of at least 21 (of 30 points) who were randomized to a 12-week cognitive rehabilitation program or standard medical management (site-specific). There were no between-group differences in any outcome measure. There also were no group differences in subgroup analyses by age, sex, education level, or baseline cognitive ability. A difference in outcomes were seen in depression scores, which improved significantly for females in the intervention group, but not for males.

Another randomized study of 54 patients by Chapman et al. (2004) evaluated the combined effect of a cognitive-communication therapy plus an acetylcholinesterase inhibitor versus drug treatment alone. A positive effect for the inhibitor cognitive rehabilitation group was found for discourse abilities, functional abilities, emotional symptoms, and overall global performance. Beneficial effects were reported up to 10 months after active intervention.

Spector et al. (2003) published an RCT on 115 patients assigned to a cognitive stimulation program or a control group. The intervention program ran for 7 weeks, and patients were only evaluated at completion. The treatment group had significantly higher scores on the principal outcome MMSE, with a group difference of 1.14 points. Differences were also significant for secondary outcomes, a quality-of-life score for AD, and an AD assessment scale. The trialists limited assessment of outcomes to the 7-week period of treatment and concluded that the intervention would need to be continued on a regular basis beyond 7 weeks.

Table 1: Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions			
					Therapy 1	Therapy 2	Therapy 3	Therapy 4
Clare et al (2019)	England, Wales	8	2013-2016	Patients with early- stage Alzheimer, vascular or mixed dementia (White, 96.4%; Black, 1.5%; Asian, 1.2%; Mixed, 0.4%; Other, 0.4%)	10 weekly goal-oriented individual cognitive rehabilitation sessions, followed by 4 maintenance sessions over 6 mos (n=281)	Treatment as usual (medication, monitoring, general psychosocial support) (n=208)	NR	NR
Amieva et al (2016)	France	40	2008-2009	Patients diagnosed with Alzheimer disease	CTT (n=170)	RT (n=172)	ICRT (n=157)	Usual medical care (n=154)
Thivierge et al (2014)	Canada	NR	2008-2011	Patients with Alzheimer disease (n=20)	ELL and SR cognitive techniques	Controls	NR	NR
Kurz et al (2012)	Germany	NR	NR	Patients with mild Alzheimer disease (n=201)	12-week cognitive rehabilitation program (n=100)	Standard medical management (site-specific; n=101)	NR	NR
Chapman et al (2004)	U.S.	NR	1999-2001	Patients with mild to moderate Alzheimer disease (n=54)	Combined cognitive-communication therapy plus an acetylcholinesterase inhibitor (n=28)	Drug treatment alone (n=26)	NR	NR
Spector et al (2003)	U.K.	23	NR	Patients with dementia	Cognitive stimulation therapy (n=115)	Control (n=86)	NR	NR

CTT: cognitive training therapy; ELL: errorless learning; ICRT: individualized cognitive rehabilitation therapy; NR: not reported; RT: reminiscence therapy; SR: spaced retrieval.

Table 2: Summary of Key Randomized Controlled Trial Results

Study	Rate of patients alive and without moderately severe to severe dementia at 24 mos	Survival rate at 24 mos	Direct measure of training	Functional Ability score at 9 mos mean (SD)	Overall cognitive functioning at 1 y	Change in MMSE scores from baseline to 7 wks
Clare et al (2019)	NR	NR	Individual goal attainment at 9 mos	NR	NR	NR
Therapy			N=205, +2.52			
Control			N=211, +0.67			
Mean Difference (95% CI)			1.70 (1.32 to 2.09)			
Amieva et al (2016)			NR	NR	NR	NR
CTT	81 (47.7%)	124 (72.9%)				
RT	78 (45.4%)	118 (68.6%)				
ICRT	85 (54.1%)	121 (77.1%)				
Control	74 (48%)	109 (70.8%)				
Thivierge et al (2014)	NR	NR		NR	NR	NR
Therapy			86.78			
Control			81.12			
Kurz et al (2012)	NR	NR	NR		NR	NR
Therapy				0.729+/- 1.82		
Control				0.857+/- 1.59		

Study	Rate of patients alive and without moderately severe to severe dementia at 24 mos	Survival rate at 24 mos	Direct measure of training	Functional Ability score at 9 mos mean (SD)	Overall cognitive functioning at 1 y	Change in MMSE scores from baseline to 7 wks
p-value				.64		
Chapman et al (2004)	NR	NR	NR	NR		NR
Therapy					24.62	
Control					26.96	
Spector et al (2003)	NR	NR	NR	NR	NR	
Therapy						0.9
Control						-0.4
p-value						.044

CI: confidence interval; CTT: cognitive training therapy; ICRT: individualized cognitive rehabilitation therapy; MMSE: Mini-Mental Status Examination; RCT: randomized controlled trial; RT: reminiscence therapy; SD: standard deviation.

Table 3: Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Clare et al (2019)	4. Enrolled populations do not reflect relevant diversity				
Amieva et al (2016)	4,5. Racial and ethnic demographics for enrolled population are not reported				
Thivierge et al (2014)			4. Not the intervention of interest		1,2. Follow-up only 24 wks
Kurz et al (2012)					1,2. Follow-up only 9 mos

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Chapman et al (2004)					
Spector et al (2003)					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4: Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Follow-Up ^d	Power ^e	Statistical ^f
Clare et al. (2019)		1. Participants and clinical staff not blinded				
Amieva et al. (2016)	2. Allocation not concealed	1. Participants and clinical staff not blinded				
Thivierge et al. (2014)	2. Allocation not concealed	1,2. No blinding				
Kurz et al. (2012)	2. Allocation only concealed from outcome raters	1. Not blinded to treatment assignment				
Chapman et al. (2004)	1. Randomization process not described					
Spector et al. (2003)	3. Allocation concealment unclear	1,2,3. Blinding not clear				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Dementia

A 2023 Cochrane systematic review of cognitive rehabilitation including trials conducted between 2010 and 2022 focusing on outcomes related to everyday function found statistically significantly improved participant self-ratings of goal attainment related to everyday functioning both immediately following rehabilitation and after 3 to 12 months follow-up post-rehabilitation. There was less certainty regarding whether cognitive rehabilitation had a meaningful effect on quality of life. One large RCT with a goal-oriented cognitive rehabilitation program has reported significantly less functional decline on 1 of 2 functional scales and institutionalization in the cognitive rehabilitation group compared with usual care at 24 months. Studies in AD lack relevant racial and ethnic diversity.

Stroke

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional in individuals with cognitive deficits due to stroke is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to stroke.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to stroke has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Four Cochrane reviews have assessed the effectiveness of cognitive rehabilitation for recovery from stroke. The reviews evaluated spatial neglect, attention deficits, and memory deficits. The most recent updates of these reviews for these three domains made the following conclusions:

- Spatial neglect: A 2013 update identified 23 RCTs with 628 patients. There was very limited evidence for short-term improvements on tests of neglect with cognitive rehabilitation. However, for reducing disability due to spatial neglect and increasing independence, the effectiveness of cognitive rehabilitation remained unproven.
- Attention deficit: A 2013 update identified 6 RCTs with 223 patients. There was limited evidence of short-term improvement in divided attention (ability to multitask), but no indication of short-term improvements in other aspects of attention. Evidence for persistent effects of cognitive rehabilitation on attention or functional outcomes was lacking. A 2019 update identified no new trials and concluded that the effectiveness of cognitive rehabilitation for attention deficits following stroke remains unconfirmed.
- Memory deficit: A 2016 update identified 13 trials with 514 patients. There were statistically significant benefits in subjective measures of memory in the short-term (i.e., the first assessment measurement after the intervention) but not in the longer term (i.e., the second assessment measurement after the intervention). The quality of the evidence ranged from very low to moderate; there was poor quality of reporting in many studies, lack of consistency in the choice of outcome measures, and small sample sizes.

Gillespie et al (2015) published an overview of Cochrane reviews and a more recent RCT assessing rehabilitation for post-stroke cognitive impairment. Data from 44 trials (N=1,550) were summarized. In addition to post-stroke spatial neglect and attention and memory deficits (addressed in the 4 Cochrane publications previously described), post-stroke perceptual disorders, motor apraxia, and executive dysfunction were reviewed. Conclusions were:

- Very little high-quality evidence exists for the effectiveness of cognitive rehabilitation for post-stroke cognitive deficits.
- Current evidence has shown that cognitive rehabilitation for spatial neglect, attention deficits, and motor apraxia improve standardized assessments of impairment immediately after treatment. However, the durability and clinical significance of these improvements are unclear.
- Evidence for the effectiveness of cognitive rehabilitation for post-stroke memory deficits, perceptual disorders, or executive dysfunction was not identified.

Randomized Controlled Trials

Zucchella et al. (2014) conducted an assessor blinded RCT of comprehensive cognitive rehabilitation, combining computer training and metacognitive strategies within 4 weeks after stroke. Of 288 consecutive stroke survivors admitted to a neurorehabilitation unit in Italy, 92 (32%) met inclusion criteria and were randomized to cognitive rehabilitation (n=45) or control (n=47). At the end of treatment (i.e., at week 4), statistically significant differences were found between groups on some measures of memory and visual attention. The clinical significance of these short-term outcomes is unclear.

Section Summary: Stroke

Recent systematic reviews have generally reported limited effects of cognitive rehabilitation in stroke individuals.

Multiple Sclerosis (MS)

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional in individuals with cognitive deficits due to multiple sclerosis (MS) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to MS.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to MS has varying lengths of follow-up, ranging from 6 months to 1 year. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 1 year of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Three Cochrane reviews have evaluated cognitive rehabilitation for patients with MS and cognitive impairments. In an update, das Nair et al. (2016) included 15 studies with 989 patients. There were no differences in subjective reports of memory functioning or mood. There was some evidence of a significant effect by intervention on objective assessments of memory in both the immediate and long-term follow-up and quality of life in intermediate follow-up. However, this effect on objective memory

outcomes and quality of life was no longer statistically significant when studies at high-risk of bias were excluded.

Rosti-Otajarvi and Hamalainen (2014) conducted a Cochrane review of neuropsychological rehabilitation in MS. Twenty RCTs met inclusion criteria (N=986 patients), including 7 of the 8 trials in the das Nair et al (2016) Cochrane review. Overall quality and comparability of included trials were low due to methodologic limitations and variations in interventions and outcome measures across trials, respectively. In meta-analysis, statistically significant improvements in memory span (based on 2 low-quality trials, n=150 patients; standardized mean difference, 0.54; 95% CI, 0.20 to 0.88; p=.002; $I^2=0\%$) and working memory (3 very low-quality trials, n=288 patients; standardized mean difference, 0.33; 95% CI, 0.09 to 0.57; p=.006; $I^2=0\%$) were observed with cognitive training compared with controls. Statistically significant improvements in attention, information processing speed, immediate verbal memory, executive functions, and depression were not observed.

Redero et al (2023) reported results of a systematic review of neuropsychological rehabilitation in patients with relapsing-remitting MS including studies published between 2012 and 2022, 15 studies (N ranging from 9 to 98) were included; 12 were RCTs, 2 were quasi-experimental and 1 had unclear allocation method. The authors found that most of the RCTs published from 2012 to 2022 evaluated rehabilitation interventions delivered through validated computer software. Therefore they are not relevant to this review.

Table 5: Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	Intervention	N (Range)	Design	Duration
Rosti-Otajarvi et al (2014)	1993-2013	20	Patients with MS	Neuropsychological rehabilitation	986 (15-240)	RCTs and quasi-randomized trials	Mean 9.5 wks
Das Nair et al (2016)	1993-2015	15	Patients with MS	Cognitive rehabilitation	989 (19-240)	RCTs and quasi-randomized trials	NR

MS: multiple sclerosis; NR: not reported; RCT: randomized controlled trials;.

Table 6: Systematic Review & Meta-Analysis Results

Study	Memory Span Improvement (SMD)	Working Memory Improvement (SMD)	Objective Assessment of Memory (SMD)	Activities of Daily Living (SMD)
Rosti-Otajarvi et al (2014)	0.54	0.33	NR	NR
95% CI	0.2 to 0.88	0.09 to 0.57	NR	NR
p-value	.002	.006	NR	NR

Study	Memory Span Improvement (SMD)	Working Memory Improvement (SMD)	Objective Assessment of Memory (SMD)	Activities of Daily Living (SMD)
Das Nair et al (2014)	NR	NR	0.26	-0.33
95% CI	NR	NR	0.03 to 0.49	-0.63 to -0.03
p-value	NR	NR	.03	.03

CI: confidence interval; NR: not reported; SMD: standardized mean difference.

Randomized Controlled Trials

Chiaravalloti et al. (2021) completed a randomized controlled trial and reported new learning and memory (NLM) impairments are common in multiple sclerosis (MS), negatively impacting daily life. Few studies seek to remediate these deficits to improve everyday functioning. Self-generation, spaced learning and retrieval practice have been shown to improve NLM in healthy persons and have been incorporated into an 8-session treatment protocol, Strategy-based Training to Enhance Memory (STEM). STEM teaches participants about each of the techniques, how to apply them in daily life and provides practice. Participants are taught to restructure a memory-demanding situation to optimize self-generation, spaced learning and retrieval practice. This pilot double-blind, placebo-controlled, randomized clinical trial (RCT) tested the efficacy of STEM in 20 learning-impaired participants with clinically definite MS (9 treatment, 11 control). Significant treatment effects were noted on self-report measures of daily functioning (primary outcome). Objective neuropsychological testing approached significance, showing a medium-large effect on verbal NLM. Results suggest that STEM may improve everyday functioning in individuals with MS. A full-scale RCT is warranted to validate findings in a larger sample so that findings may be generalized to the broader MS community.

The largest and longest-term RCT conducted in people with MS receiving cognitive rehabilitation was published by Lincoln et al. (2020) (see the table below). It was a multicenter, observer-blinded RCT in patients with relapsing-remitting (65%), primary progressive (10%) or secondary progressive MS (25%). Participants were recruited between 2015 and 2017 and randomized to 10 weekly sessions of a group cognitive rehabilitation program (n=245) or usual care (n=204). Outcomes were assessed at 6 and 12 months after randomization. Although there were small improvements in mood and everyday memory problems, there were no significant long-term benefits in cognitive abilities, fatigue, employment, or quality of life (see the tables below). Its main methodological limitation was that there was no sham cognitive rehabilitation group and participants were not masked to treatment assignment (see the tables below).

Table 7: Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants²	Interventions¹	
					Active	Comparator

Lincoln et al (2020); CRAMMS RCT	England	5	2015-2017	People aged 18 to 69 yrs with MS who reported cognitive problems in daily life	10 weekly sessions of cognitive rehabilitation, delivered by an Assistant Psychologist to groups of 4 to 6 participants; standardized content defined by a treatment manual; n=245	Usual care, n=204
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CRAMMS: Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis; MS: multiple sclerosis.

Table 8: Summary of Key Randomized Controlled Trial Results

Study	Multiple Sclerosis Symptoms Measure	Employment Measures	Quality of Life Measures
Lincoln et al (2020)	387	382	382
	Mean MSIS (SD) Psychological score at 12 mos	Any employment at 12 mos	Mean (SD) EQ-5D visual analog at 12 mos
Cognitive rehabilitation	22.2 (6.1)	60 (29%)	61.6 (19.3)
Usual care	23.4 (6.0)	50 (29%)	59.7 (20.0)
Relative measure	Adjusted mean difference, -0.6; 95% CI, -1.5 to 0.3	Odds ratio, 0.99; 95% CI, 0.60 to 1.63	Adjusted mean difference, 2.6; 95% CI, -0.9 to 6.0

CI: confidence interval; EQ-5D: European Quality-of-Life Five-Level; MSIS: Multiple Sclerosis Impact Scale; SD: standard deviation;.

Table 9: Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Lincoln et al. (2020)			3. Delivery not similar intensity as intervention		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10: Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Lincoln et al (2020)		1. Participants and assistant psychologists aware of allocation				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Several additional smaller, single-center and shorter-term RCTs have been conducted (see the table below). These RCTs are heterogeneous in terms of MS type, intervention format, frequency and duration, and outcome assessment methods. Overall, results of the RCTs have been mixed, with the majority of benefits for cognitive rehabilitation only observed in the short-term and either not measured or not sustained in the longer-term.

Table 11: Summary of Small and Shorter-Term Trials in Individuals with Multiple Sclerosis Undergoing Cognitive Rehabilitation

Author Year	N	MS type	Intervention	Comparator	Summary of Results
Nauta et al (2023)	110	66% relapsing-remitting; 17% secondary progressive; 12% primary progressive	9 weekly group-based sessions of 2.5 hours	Enhanced treatment as usual: 1 individual appointment with MS specialist nurse focused on psycho-education	CRT alleviated cognitive complaints immediately after rehabilitation, but benefits in cognition did not persist to 6 months. At 6-month follow-up, CRT showed benefits on personalized cognitive goals

					(goals concerning daily life problems identified at baseline for each participant) and processing speed.
Brissart et al (2020)	110	MS; 22% relapsing-remitting MS	13 2-hour extended cognitive rehabilitation sessions delivered over 6 mos	13 2-hour non-cognitive exercise sessions delivered over 6 mos	Some improvement was observed in the cognitive rehabilitation group in measures of memory function, but there were no differences between groups in executive function or quality of life measures at 6 to 9 mo follow-up.
Chiaravalloti et al (2005)	117	Primarily relapsing-remitting MS	8 biweekly 45-min cognitive rehabilitation sessions	Control sessions with the same therapist at the same frequency, engaging in nontraining tasks (eg, reading and recalling a story)	Mixed at 5 and 11 wks. No statistical differences between groups in new learning or emotional functioning. Self-reported improvements in memory were greater in the cognitive rehabilitation group at both time points. Results for other neuropsychological assessments were not reported.
Chiaravalloti et al (2013)	88	MS	10 biweekly, 45- to 60-min sessions of modified SMT	Control sessions with the same therapist at the same frequency, engaging in nontraining tasks (eg, reading and recalling a story)	Mixed effects at 5 wks, but majority of benefits were not sustained at 6 months. At 5 wks, there were significant improvements in learning efficiency, objective everyday memory, general

					contentment (subjective everyday cognition and emotional functioning), apathy, and executive dysfunction, but not awareness level, depression, or anxiety. At 6-mos follow-up, the only persistent between-group difference was general contentment.
Rosti-Otajarvi et al (2013) Mantynen et al (2014)	102	Relapsing-remitting MS and attentional deficits	strategy-oriented neuropsychological rehabilitation (13 weekly 60-min sessions)	No intervention	Although no improvement in cognitive performance at wk 13 or at 6 mos, there was improvement in perceived cognitive deficits at both time points and in a subset of patients who completed 1-y follow-up (83% completers in the therapy group vs. 67% in the control group). ^a
Hanssen et al (2016)	120	MS	4 wks of multidisciplinary cognitive rehabilitation	Standard rehab	Improvement on a health-related quality of life measure relating to psychological health, but no differences in executive function at 4 or 7 mos.
Shahpouri et al (2019)	56	Primarily relapsing remitting (70%)	10, 2-h individualized sessions held every 7-10 days - approaches developed considering the severity of cognitive	Same number and duration of sessions, but content was not supporting	Memory, attention, quality of life, and depression were all significantly improved within 3

			impairment and with the aim of optimization of the residual functions	cognitive rehabilitation	mos after study initiation.
Chiaravalloti et al (2019)	20	Learning-impaired participants with primarily relapsing remitting MS (65%)	STEM: 2, 30 to 45 min sessions per wk for 4 wks; guided practice of a set of structured and standardized tasks to train individuals on self-generation, spaced-learning, and retrieval practice.	Participants met individually with the therapist at the same frequency and locations as the treatment group, engaging in non-training oriented tasks.	Although STEM improved measures of subjective cognitive function outcomes immediately following the intervention, it did not lead to improved performance on objective neuropsychological functioning.

MS: multiple sclerosis; SMT: Story Memory Technique; STEM: Strategy-based Training to Enhance Memory.

^a Due to the possibility that dropout was related to the outcome of interest (e.g., patients with perceived cognitive decline might have been more likely to drop out), findings should be interpreted cautiously.

Section Summary: Multiple Sclerosis (MS)

Although numerous RCTs have investigated cognitive rehabilitation in MS, large, high-quality trials are lacking. The ability to draw conclusions based on the overall body of evidence is limited by the heterogeneity of patient samples, interventions, and outcome measures. Further, results of the RCTs evaluated are mixed, with positive studies mostly reporting short-term benefits. Evidence for clinically significant, durable improvements in cognition is currently lacking.

Post-Acute Cognitive Sequelae of SARS-CoV-2 Infection

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation in individuals with cognitive deficits due to post-acute sequelae of SARS-CoV-2 infection (PASC).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to PASC infection. The Centers for Disease Control and Prevention define the post-acute period as symptoms persisting at four or more weeks following infection with SARS-CoV-2.⁵¹ The World Health Organization developed the following consensus case definition of 'post COVID-19 condition': individuals with "a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time."

While subjective reports of cognitive impairment (i.e., 'brain fog') have been reported by individuals not requiring hospitalization,⁵³ current understanding of objective cognitive sequelae of COVID-19 is predominantly limited to individuals who required hospitalization. Ceban et al (2022) conducted a meta-analysis of 43 studies with 12 or more weeks follow-up that reported a 22% overall prevalence of cognitive impairment (95% CI, 17% to 28%; I²=98%; N=13232). Subjectively ascertained cognitive impairment (e.g., patient self-report) was reported in 18% of patients (95% CI, 12% to 24%; I²=97.9%; 31 studies), which was significantly lower than in studies with objective ascertainment of cognitive status utilizing validated tools (36%; 95% CI, 27% to 46%; I²=94.9%; 12 studies; p=.002). No significant difference in cognitive symptom prevalence was found in subgroup analyses of hospitalized versus non-hospitalized patients (30% versus 20%; p=.096) or patients with < 6 months versus ≥ 6 months of follow-up (22% versus 21%; p=.794).

Objective cognitive deficits have been reported for verbal fluency, attention, working memory, processing speed, executive functioning, learning, and memory - with no clear pattern of cognitive impairment across studies. While cognitive impairment following intensive treatment of critical illness is not a new phenomenon, the disease course of cognitive impairment experienced by individuals with post-acute sequelae of SARS-CoV-2 infection is an ongoing research priority.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The natural history of PASC has not been fully categorized, particularly in non-hospitalized individuals. A prospective study measuring cognitive performance among patients who experienced mild disease noted that declines in cognitive scores reported at 6 months spontaneously resolved at 18-month follow-up. Persistent cognitive deficits have been reported in 16% of COVID-19 survivors at 1 year who were treated in the intensive care setting. Therefore, at least 1 to 2 years of follow-up may be considered necessary to demonstrate efficacy and to fully observe outcomes.

The American Academy of Physical Medicine and Rehabilitation Multi-Disciplinary PASC Collaborative issued a consensus guidance statement recommending that patients should be screened for signs of cognitive symptoms using validated tools and instruments, such as the Montreal Cognitive Assessment (MoCA) or MMSE. Additional neuropsychological measures used to assess cognitive and behavioral alterations in PASC are described by De Luca and coworkers and are listed on the CDC website.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

No published randomized controlled trials of cognitive rehabilitation post-COVID-19 were identified. However, Hagen et. al. (2022) has published the protocol for an ongoing randomized controlled trial with a planned primary endpoint of the Metacognition Index of the self-reported Behavior Rating Inventory of Executive Function - Adult Version, as measured at six months post-treatment.

Saxon et. al. (2025) conducted a retrospective cohort study of 70 consecutive adults with long-COVID. The majority of study participants were women (77%), who were White (69%), and had an average age of 46.5 years. The majority were never hospitalized for COVID-19 (83%). The study found mixed results. While some improvement in self-reported functional cognition outcomes were observed, this was limited by concomitant anxiety and not replicated by objective memory measures.

Section Summary: Post-Acute Cognitive Sequelae of SARS-CoV-2 Infection

No randomized controlled trial evidence on the efficacy of cognitive rehabilitation programs in patients with PASC was identified. Controlled prospective studies in well-defined patient populations with sufficient follow-up duration are necessary to evaluate net health outcomes. Ongoing research continues to elucidate the natural course of cognitive symptoms associated with PASC.

Other Cognitive Deficit Conditions

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation in patients with cognitive deficits due to Alzheimer's disease, autism spectrum disorder (ASD), coma, epilepsy, post encephalopathy, or cancer or previous cancer treatments.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to Alzheimer's disease, autism spectrum disorder (ASD), coma, epilepsy, post encephalopathy, or cancer or previous cancer treatments.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to Alzheimer's disease, autism spectrum disorder (ASD), coma, epilepsy, post encephalopathy, cancer or previous cancer treatments has varying lengths of follow-up, ranging from 2 to 6 months. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 6 months of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Coma

Cognitive rehabilitation for individuals who are in a coma is also known as coma stimulation, "Responsiveness Program" (cognitive remediation of comatose persons), coma arousal program/therapy, sensory stimulation and multi-sensory stimulation programs for coma and persistent vegetative state.

Systematic Review

In 2020, Li et al. completed a systematic literature review on sensory stimulation to improve arousal in comatose individuals after sustaining a TBI. Ten studies were eligible and included in the analysis. Post TBI patients with severe consciousness disorders who utilized sensory stimulation with identified protocols, assessment tools, and assessments by standard scales and instruments. Consistent with the 2002 Cochrane review, this review concluded that although there appears to be some evidence that sensory stimulation may increase arousal in comatose individuals, "high-quality clinical trials are needed to establish standard SS [sensory stimulation] protocols."

In 2002, a Cochrane systematic review was completed by Lombardi et al. to assess the effectiveness of sensory stimulation programs in individuals in a coma or vegetative state. The selection criteria was randomized or controlled trials that compared sensory stimulation programs with standard rehabilitation in patients in coma or vegetative state which ultimately included 68 individuals from 3 studies. The authors concluded, "the overall methodological quality was poor and studies differed widely in terms of outcomes measures, study design and conduct." Therefore, there was not "any quantitative synthesis but reviewed results of available studies qualitatively." The review found there is no strong evidence to determine whether sensory stimulation benefits people in comas."

Epilepsy/Seizure Disorders

Farina et al. (2015) in Italy conducted a systematic review of the literature on cognitive rehabilitation for epilepsy. Literature was searched through December 2013, and 18 articles of different types (reviews, methodologic papers, case reports, experimental studies) were identified. Studies were heterogeneous for patient characteristics (type of epilepsy, type of previous treatment [surgery, antiepileptic drugs]), intervention modalities (e.g., holistic, focused) and duration, and outcome measures. Reviewers considered the overall quality of evidence to be moderate to low, and results inconsistent (e.g., not all

studies showed benefit; some showed greater benefit in left-sided seizures, and others showed greater benefit in right-sided seizures).

The 2013 updated systematic review⁷ by American Congress of Rehabilitation Medicine (ACRM) evaluated cognitive rehabilitation in epilepsy. Based on 2 comparative studies (1 randomized; N=156), ACRM recommended cognitive rehabilitation for attention and memory deficits as a “possibly effective” practice option for seizure-related attention and memory deficits. The RCT by Engelberts et al (2002) prospectively enrolled 50 patients with focal seizures who were receiving carbamazepine monotherapy. Patients were randomized to a retraining method aimed at retraining impaired cognitive functions (n=19), to a compensation method aimed at teaching compensatory strategies (n=17), or to a wait-list control group (n=8). Both interventions focused on divided attention (ability to multitask). At 6-month follow-up, performance on cognitive tests improved more in both intervention groups than in the control group. No differences in inhibitory capacity were observed. Self-reported cognitive complaints, absentmindedness, and quality of life improved more with cognitive rehabilitation. Overall, the different rehabilitation methods were similarly effective.

Helmstaedter et al. (2008), in a nonrandomized study, assessed the short-term effects of cognitive rehabilitation on memory deficits in 2 retrospective, matched cohorts of temporal lobe epilepsy surgical patients. Mean age was 36 years. Mean age at onset of epilepsy was 4 years, and mean intelligence quotient (IQ) was 105. Patients who received cognitive rehabilitation (n=55) participated in a 1-month program comprising educational sessions about brain function and cognitive exercises. A cohort of 57 patients received no cognitive rehabilitation. Statistically significant improvements in verbal learning and recognition were observed in right-resected patients who received cognitive rehabilitation. Cognitive rehabilitation had nonsignificant effects in left-resected patients. Study limitations included its retrospective design and baseline imbalances in patients’ memory and attention deficits (more severe deficits in the control cohort). The limited evidence base precludes conclusions about cognitive rehabilitation for this indication.

Autism Spectrum Disorder

Reichow et al. (2013) reported on a systematic review of psychosocial interventions administered by nonspecialists for children and adolescents with intellectual disability (IQ<70) or lower functioning ASD, five comparative trials in patients with ASD (total N=255 patients) who received cognitive rehabilitation, training, and support were included. Improvements in school performance and developmental outcomes were inconsistent across trials.

Wang and Reid (2013) conducted a pilot study of a novel virtual reality-cognitive rehabilitation intervention in 4 children (mean age, 7.4 years) with ASD. Children with autism, who are difficult to engage, may respond better to virtual reality approaches than to traditional cognitive rehabilitation. Mean nonverbal IQ ranged from 93 to 139. Each child viewed training programs on laptop computers equipped with tracking webcams. The child’s image and movements were projected into virtual environments where he/she was required to manipulate virtual objects. Outcomes were measures of contextual processing, defined as “the ability to determine an object’s meaning or relevance in a particular context,” and of abstraction and cognitive flexibility, with executive functions considered components of contextual processing. After 4 to 6 weeks, all children demonstrated statistically significant improvements in contextual processing and cognitive flexibility. Abstraction scores at baseline were at or close to maximum.

Eack et al. (2013) conducted a feasibility study of a comprehensive cognitive rehabilitation intervention, called Cognitive Enhancement Therapy, in 14 “high functioning” adults (mean age, 25 years) with ASD. Cognitive Enhancement Therapy, which was originally developed for patients with schizophrenia, provides social interaction and cognitive training focused on attention, memory, and problem-solving.

Mean full scale IQ of the patient sample was 118 (range, 92-157). Eleven (79%) of 14 patients completed 18 months of treatment. Statistically significant changes from baseline were observed in mean composite measures of neurocognition, cognitive style, social cognition, and social adjustment. All components of neurocognition (e.g., processing speed, working memory) improved statistically, except attention/vigilance.

Postencephalitis

The ACRM systematic review (2013) also evaluated cognitive rehabilitation for postencephalitis cognitive deficits. Eight identified studies were considered poor quality evidence and insufficient for forming conclusions.

Cancer

Cognitive rehabilitation has been investigated in three cancer-related settings: in children receiving oncological treatment with regular inpatient stays however the purpose of this medical policy is to review cognitive rehabilitation in the outpatient setting so this is not applicable to the intent of this medical policy and not included individuals with brain tumors, and cancer survivors whose cognitive deficits are attributed to cancer treatment.

Cancer Treatment: Pediatric

For children with cancer receiving cognitive rehabilitation, the evidence includes 1 small (N=46), single-center RCT by Akel et al. (2019) (see the table below). The cognitive rehabilitation was delivered in the inpatient treatment clinic of the Department of Pediatric Oncology at University Hospital in Ankara, Turkey. Cognitive skills targeted by the cognitive rehabilitation therapy included place and time orientation, internal and external spatial perception, praxis, attention, visio-motor construction, and thinking operations. Children were characterized by a mean age of 10 years and 55% were male. Cancer diagnoses included non-Hodgkin lymphoma (40%), Hodgkin lymphoma (30%) and bone tumors (30%). Outcomes were evaluated only immediately postintervention. Although compared to the routine therapy groups (Table 13), numerically larger effect sizes for change in fatigue and functional independence were reported for the cognitive rehabilitation group, it is unknown whether the differences were clinically or statistically significant as the comparative treatment effects were not calculated, and clinically significant difference were not prespecified. Significant improvements in cognitive measures were reported pre/post in the intervention group, but no data were reported for the routine therapy group on this outcome. In addition to these inadequate outcome assessment methods, interpretation of these findings are limited by other methodological shortcomings (see the tables below) including lack of blinding of participants and lack of long-term follow-up. Therefore, this evidence is not sufficient to draw conclusions on effect on health outcomes.

Table 12: Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants ²	Interventions ¹	
					Active	Comparator
Akel et al (2019)	Turkey	1	NR	Children aged 6 to 12 yrs receiving oncological treatment with regular inpatient	15 sessions of structured cognitive rehabilitation that used play to target	15 sessions of routine therapy, including relaxation training and task-oriented

				stays for non-brain tumors or brain metastasis and an MMSE for children score >24	various cognitive skills; n=25	activity of daily life training; n=21
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MMSE: Mini-Mental Status Examination; NR: not reported..

Table 13: Summary of Key Randomized Controlled Trial Results

Study	Cognitive Measures	Fatigue Measures	Functional Independence Measures
Akel et al (2019)	40	40	40
Measures	Mean total DOTCA-Ch (SD) score pre/post-intervention	Mean (SD) VAS-fatigue pre/post-intervention for post-activity/Effect size/P-value	Mean (SD) WeeFIM total score pre/post-intervention/Effect size/P-value
Cognitive rehabilitation	121.54 ± 13.18/135.36 ± 10.24	5.45 ± 1.01/1.72 ± 0.98/3.69/<.001	52.45 ± 8.90/62.68 ± 9.74/1.15/<.001
Control group	NR	3.16 ± 2.45/2.16 ± 1.79/0.41/.01	52.33 ± 9.29/53.11 ± 8.73/0.08/.068
Relative measure	NA	NR	NR

DOTCA-Ch: Dynamic Occupational Therapy Cognitive Assessment for Children; NA: not applicable; NR: not reported; SD: standard deviation; WeeFIM: Functional Independence Measure for Children; VAS: Visual Analog Scale.

Table 14: Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Akel et al (2019)			3. Delivery not similar intensity as intervention	5. Clinical significant difference not prespecified	1. Not sufficient duration for benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 15: Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
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Akel et al. (2019)		1. Participants aware of allocation			1. Power calculations not reported	4. Comparative treatment effects not calculated
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The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Brain Tumors

The 2013 ACRM systematic review evaluated cognitive rehabilitation for adults with brain tumors. In 5 case reports and case series (N=36 patients), some individuals showed benefit with various cognitive rehabilitation interventions. This evidence was considered insufficient to support any recommendations.

Zucchella et al. (2013) conducted an RCT of cognitive rehabilitation in adults after neurosurgery at a single rehabilitation facility in Italy. Time since craniotomy was not reported. Adjuvant chemotherapy or radiotherapy was not administered until after the trial. Of 109 consecutive patients screened for participation, 62 (57%) met minimum cognitive deficit and other criteria and were randomized to usual rehabilitative care with (n=30) or without (n=32) cognitive rehabilitation. Treatment sessions were held 4 times a week for 4 weeks and were comprised of 45 minutes of therapist-guided computer exercises in 6 cognitive domains (time and spatial orientation, visual attention, logical reasoning, memory, executive function) and 15 minutes of cognitive strategizing. At the end of treatment (i.e., at week 4), statistically significant improvements in visual attention and verbal memory were observed in the treatment group compared with controls. Improvements in logical reasoning and executive function were not statistically significant. Limited study follow-up makes the clinical significance of these findings unclear.

Cancer Survivors

Systematic Reviews

Fernandes et al. (2019) published a systematic review of cognitive rehabilitation programs in adults with non-CNS cancers. It included 1,124 participants (n range, 11 to 242) from 19 studies published between 2007 and 2018, of which the majority were RCTs (N=12). Waitlist was the most common comparator in the RCTs. As with the previous reviews, most studies in this review assessed the effects of the intervention immediately postintervention or at short-term follow-up (≤ 6 months), and most trials were conducted in breast cancer survivors. This review did not perform any meta-analyses. Findings across the studies were mixed. Although the review reported that among the RCTs and nonrandomized controlled studies “87% found short-term improvements on at least one objective cognitive measure,” this finding primarily pertained to measurements taken immediately postintervention. In contrast, in the longest-term (26-month follow-up) and largest trials (n=242) included, there were no significant effects on various objective cognitive measures. Only 63% of studies found improvements in short-term quality of life measures and none found any improvements in functional outcomes. The authors noted they provided specific recommendations to facilitate future research and integration in this field. An important limitation of all studies is that participants were not blinded to group assignment.

Zeng et al. (2016) published a meta-analysis of a neuropsychologic intervention for cognitive function in cancer survivors. Three case-control studies and 7 RCTs with 433 patients (range, 22 to 98 patients), published between January 2010 and September 2015, were included. Most trials assessed the effects of the intervention immediately postintervention or at short-term follow-up (≤ 6 months). More than half of the trials were conducted in breast cancer survivors. Three trials assessed the effects of cognitive rehabilitation programs and the weighted mean difference for the intervention effect at postintervention follow-up was -0.19 (95% CI, -2.98 to 2.61). The authors concluded the findings from this meta-analysis indicate that neuropsychological interventions can improve cognitive function in non-CNS cancer survivors and support the need for future research. However, the conclusion from this meta-analysis was based on trials with small sample sizes. Future research should be conducted using a larger sample size. Relevant clinical implications were discussed accordingly.

The 2013 systematic review by ACRM evaluated cognitive rehabilitation for cognitive impairments in adult and pediatric cancer survivors. A German RCT, by Poppelreuter et al. (2008), showed no benefit with cognitive rehabilitation in 157 adult inpatients who had cognitive impairments after hematopoietic cell transplantation. In children and adolescents, 2 prospective, comparative studies (1 an RCT by Butler et al [2008]) evaluated cognitive rehabilitation in treatment survivors (resection, cranial radiotherapy, and/or chemotherapy) involving the CNS (N=192 patients). Reviewers concluded that process-based cognitive rehabilitation techniques (e.g., strategy acquisition, corrective feedback) were "probably effective" in treating attention and memory deficits in these patients. However, the Butler et al (2008) RCT had several methodologic limitations. It randomized 161 pediatric survivors of treatment for brain tumors, leukemia, bone marrow transplant involving total body irradiation, and non-Hodgkin lymphoma 2:1 to a cognitive remediation program (n=108) or wait-list controls (n=53). Documented attentional deficit was required for trial eligibility. The cognitive remediation program comprised 2-hour weekly sessions of practice, strategy acquisition, and cognitive-behavioral interventions for up to 20 sessions. Both groups were assumed to receive special education services if needed; this factor was not analyzed in the results. The primary outcome was change from baseline in 5 investigator-developed, multi-test indices (academic achievement, brief focused attention, working memory, memory recall, vigilance) at approximately 6 months after baseline assessments. These indices incorporated results from 11 validated scales completed by blinded study assessors and unblinded parents, teachers, and patients. Mean patient age was 11 years. Sixty percent of patients in the cognitive remediation group completed the entire program; 80% completed 75% (15 sessions). Six-month follow-up was differential between groups (83% in the cognitive remediation group vs. 98% in the control group). The analysis was intention-to-treat. The statistically greater improvement was observed in the cognitive remediation group than in the control group only in academic achievement, although the treatment effect was small (standardized mean difference, 0.24) and of uncertain clinical relevance. Given the lack of improvement on the neurocognitive scales, it did not appear that improved academic achievement was due to improved neurocognitive function.

Randomized Controlled Trials

For cancer survivors receiving cognitive rehabilitation, the evidence published subsequent to the above-described systematic reviews includes 1 small (N=25), single-center RCT by Richard et al. (2019) (The table below). This RCT randomized 46 participants to either Goal Management Training, a Brain Health Program active control that promotes general brain health, or a wait-list control group. The study reported outcomes immediately following the 8-week treatment period and 4 months following treatment completion. Participants had a mean age of 48 years, and 60% were male. Disease characteristics included various tumor types (28% meningioma, 32% low-grade glioma, 24% high-grade glioma) with a mean duration of 23 years since diagnosis. The most common cancer treatment was surgical resection (72%). The most recent type of treatment was whole-brain radiotherapy, which occurred a mean of 3 years prior. The primary outcome measure was change on an investigator-developed executive

functioning test composite score. Although compared to the active and wait-list control groups, improvements in executive functioning and real-life functional goal attainment were significantly greater for the Goal Management Training group immediately following treatment, the improvement was only maintained at the 4-month follow-up period for the executive functioning outcome (see the table below). No quality-of-life measure was reported. Although the improved executive functioning outcome is encouraging, numerous important study and relevance shortcomings seriously limit the interpretation of these findings (see the table below). For example, the clinical significance of the executive functioning outcome is unclear as it is not an established measure, and its validity is unknown. Additionally, as the executive functioning outcome was not evaluated using an intent-to-treat analysis and excluded a larger proportion of wait-list control group participants than in the Goal Management Training groups (33% vs. 9%), we cannot rule out that the results were biased based on the high and differential exclusions. In addition, interpretation of these findings are limited by other methodological shortcomings including lack of blinding of participants and lack of long-term follow-up. Therefore, this evidence is not sufficient to draw conclusions on effect on health outcomes.

Table 16: Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants ²	Interventions ¹	
					Active	Comparator(s)
Richard et al (2019)	Canada	1	NR	Adults aged ≥18 yrs with a diagnosis of a primary brain tumor who were ≥3 mos postradiation or surgery with persistent cognitive dysfunction (≤1 SD below executive function testing norms)	8 weekly 2-h individual sessions of a structured and standardized GMT program, a behavioral intervention delivered by a clinical neuropsychologist, with homework between sessions; n=11	8 weekly 2-h individual sessions of a psycho-educational BHP, also with homework of more general “brain challenges”; n=8 Waitlist control; n=6

BHP: brain health program; GMT: goal management training; NR: Not reported; SD: standard deviation.

Table 17: Summary of Key Randomized Controlled Trial Results

Study	Cognitive Measures ^a	Functional Outcomes	Quality of Life Outcomes
Richard et al (2019)	19	19	19
Measures	Mean change (SD) in the Executive Functioning Composite at 4 mos follow-up	Functional goal attainment at 4 mos	NR
GMT	+0.69 (0.51)	NR	
BHP	+0.13 (0.50)	NR	NR
WAIT	-0.07 (0.44)	NR	NR

P-value for time-by-group interaction	.046	.064	NR
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^aThe Executive Functioning Composite score was calculated by averaging component measure z-scores at each time point across a number of tests including the Trail Making Test B, Test of Everyday Attention (TEA), Sustained Attention to Response Task (SART), Behavioral Assessment of the Dysexecutive Syndrome (BADS), and the Hotel Test.

BHP: Brain Health Program; GMT: Goal Management Training; WAIT: Wait-list control; NR: Not Reported; SD: standard deviation.

Table 18: Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Richard et al (2019)				1. Key health outcomes not addressed 4. Not establish and validated measurements 5. Clinical significant difference not prespecified	1. Not sufficient duration for benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 19: Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Richard et al (2019)	3. Allocation concealment unclear	1. Participants aware of allocation		1. High loss to follow-up or missing data (GMT=9%, BHP=25%, WAIT=33%) 6. Not intent to treat analysis (per protocol for noninferiority trials).	1. Power calculations not reported	

BHP=Brain Health Program; GMT: Goal Management Training; WAIT: Wait-list control.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Other Cognitive Deficit Conditions

Systematic reviews of cognitive rehabilitation for a number of conditions, including Alzheimer’s disease, autism spectrum disorder (ASD), coma, epilepsy, post encephalopathy, cancer or previous cancer treatments have generally concluded that there is no strong evidence supporting the efficacy of cognitive rehabilitation. Randomized trials of cognitive rehabilitation have numerous methodologic flaws that preclude strong conclusions about its efficacy.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input

In response to requests, input was received from three physician specialty societies and 5 academic medical centers while this policy was under review in 2015. Input was mixed on cognitive rehabilitation for patients with stroke, multiple sclerosis, brain tumors, or cognitive impairments after previous treatments for cancer. While input was not specifically requested for TBI, due to strong support provided in 2009 and no signals of any subsequent evidence or clinical practice changes, the American Association of Physical Medicine & Rehabilitation voluntarily and additionally reasserted its position of support for cognitive rehabilitation after TBI.

2009/2010 Input

In response to requests, input was received from 2 physician specialty societies and 5 academic medical centers while this policy was under review in 2010. The strongest support was for the use of cognitive rehabilitation as part of the treatment of those with TBI. The level of support varied for other diagnoses (e.g., use in post-stroke patients).

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology (AAN)

In 2016 (updated in 2023), the AAN released their “Practice Guideline Update: Disorders of Consciousness” makes no reference to sensory stimulation, cognitive rehabilitation, or coma stimulation as a treatment modality.

American Academy of Physical Medicine and Rehabilitation (AAPM&R)

In 2021, the American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Collaborative issued a consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with PASC. PASC cognitive symptom assessment and treatment recommendations are summarized in the table below.

Table 20: Post-Acute Sequelae of SARS-CoV-2 Infection Cognitive Symptom Assessment and Treatment Recommendations^a

Assessment Recommendations	
Recommendation #	Statement
1	"Patients should be screened for signs of cognitive symptoms using validated tools and instruments."
2	<p>"Patients should be evaluated for conditions that may exacerbate cognitive symptoms and warrant further testing and potential subspecialty referral. [...] Particular areas include:</p> <ul style="list-style-type: none"> • Sleep impairment • Mood, including anxiety, depression, and posttraumatic stress disorder • Fatigue • Endocrine abnormalities • Autoimmune disorders <p>Note: Patients often report dissatisfaction with their care because of their persistent symptoms being attributed to psychological factors. It is important to note that mood disorders may be secondary to persistent medical conditions or one of many factors leading to cognitive symptoms."</p>
3	"Patients should have a thorough neurological examination to identify focal neurological deficits."
3a	"For those patients identified with new or worsening focal neurological deficits (including new or worsening cognitive symptoms) an emergent evaluation is warranted; neuroimaging should be considered."
4	"The following basic lab workup should be considered to screen for reversible factors contributing to cognitive symptoms. The initial lab workup in new patients or those without lab workup in the 3 months prior to visit including complete blood count, vitamin B12, thiamine, folate, homocysteine, 1,25-dihydroxy vitamin D, magnesium, liver function tests, comprehensive metabolic panel thyroid function tests (thyroid stimulating hormone, free T3, free T4). In high-risk patients, one may consider syphilis rapid plasma regain and human immunodeficiency virus testing [...]"
5	<p>"Clinicians should conduct a full patient history with review of preexisting conditions and comprehensive medication and supplement review for those that may contribute to cognitive symptoms.</p> <p>Of note, patients with PASC often present on antihistamine, anticholinergic, and antidepressant/anti-anxiety medications that can contribute to cognitive symptoms."</p>
5a	"Clinicians should validate patient history through the collection of collateral history, including preexisting function and conditions, from care team/primary care, patient family or care partner, or close contact as available."
6	"Clinicians should assess impact of cognitive symptoms using standardized patient-reported assessments, to include activities of daily living, instrumental activities of daily living, school, work and avocational (ie, hobbies), and quality of life."

Treatment Recommendations	
Recommendation #	Statement
1	"For patients who screen positive for cognitive symptoms, refer to a specialist (ie, speech-language pathologist, occupational therapist, neuropsychologist) with expertise in formal cognitive assessment and remediation."
2	"Treat, in collaboration with appropriate specialists, underlying medical conditions, such as pain, insomnia/sleep disorders (including poor sleep hygiene), and mood disorders that may be contributing to cognitive symptoms."
3	"Complete, in collaboration with patient primary care provider, medication polypharmacy reduction, weaning or deprescribing medications if medically feasible with emphasis on medications that may impact cognition."
4	"Reinforce sleep hygiene techniques including nonpharmacologic approaches as first line of sleep remediation."
5	"Similar to patients experiencing "physical" fatigue, patients should be advised to begin an individualized and structured, titrated return to activity program."
5a	"For patients who achieve a return to their normal, daily activities, regular exercise (at least 2–3 times/week of aerobic exercise) may be effective in improving cognition and also contribute to improved sleep patterns."
5b	"Frequent assessment of the impact of return to normal, daily activities (including school, work, driving, operating heavy machinery, etc.) is recommended to ensure that symptoms do not flare and exercise is tolerated."

^a Adapted from Fine et al (2021).

In 2023, the American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Collaborative issued a consensus guidance statement on the assessment and treatment of neurologic symptoms in patients with PASC. PASC neurologic symptom assessment and treatment recommendations are summarized in the table below.

Table 21. Post-Acute Sequelae of SARS-CoV-2 Infection Neurologic Symptom Assessment and Treatment Recommendations^a

Assessment Recommendations	
Recommendation #	Statement
1	"Clinicians should conduct a full patient history including a review of predisposing comorbidities, prior neurologic symptoms or disorders, relevant hospitalizations, time course and severity of COVID-19 infection(s), COVID-19 treatments, vaccines/boosters, pertinent family history, and social history."
2	"Clinicians should perform a thorough neurological examination to identify focal neurological deficits."
3	"Evaluate for medication and supplement use that may impact signs, symptoms, or assessment parameters"

4	"The following basic lab workup should be considered in new patients or for those without a lab workup in the 3 months prior to the visit: complete blood count with differential; chemistries including renal and hepatic function tests, thyroid stimulating hormone, c-reactive protein, erythrocyte sedimentation rate, vitamins B1, B6, B12, and D, magnesium, and hemoglobin A1c (HbA1c)."
5	"Assess for history of previous and/or current alcohol and substance use, current diet and exercise habits, physical and cognitive activity levels, and social determinants of health (eg, housing, employment, family, insurance, access to community resources, social stressors, etc.)"
6	"Assess for changes in basic and instrumental activities of daily living, including participation at work, school, community avocational (ie, hobbies) activities."
7	"On initial evaluation, obtain standardized measures of activity performance to compare to normal control values and to guide the initial activity prescription. Repeat the standardized measures of activity performance at follow-up visits to quantify functional changes and guide progression of the activity prescription."
Treatment Recommendations	
Recommendation #	Statement
1	"In collaboration with primary care or appropriate specialist treat underlying medical conditions, such as pain, psychiatric, renal/endocrine, cardiovascular, neurological, respiratory, etc., which may be contributing to neurologic symptoms."
2	"In collaboration with primary care or appropriate specialist, consider polypharmacy reduction, weaning or deprescribing medications and supplements where medically feasible."
3	"For patients who achieve a return to their daily activities, consider recommending regular physical activity as tolerated, which may be effective in improving many neurologic symptoms and also contribute to improved sleep patterns."
4	"For patients with neurologic sequelae affecting gait, mobility, cognitive status or activities of daily living, consider referral to physical medicine and rehabilitation physician and/or allied health professionals (e.g., physical therapy, occupational therapy, speech language pathology and social work) for patient-specific recommendations to increase function and independence. To optimize functional outcomes, allied health professionals should preferably be familiar with treating sensorimotor deficits, autonomic dysfunction, and post-exertional fatigue."
5	"Provide counseling, referrals to community resources, and education for risk factor modification in the areas of: alcohol and substance use; healthy dietary pattern and hydration; return to activity, as tolerated; medications and supplements; sleep hygiene; social determinants of health."

^a Adapted from Melamed et al (2023).

American Congress of Rehabilitation Medicine (ACRM)

In 2013, based on a systematic review, the American Congress of Rehabilitation Medicine recommended process-based cognitive rehabilitation strategies (e.g., attention process training, strategy acquisition and internalization, self-monitoring, corrective feedback) to treat attention and memory deficits in children and adolescents with brain cancers who undergo surgical resection and/or radiotherapy. The strength of

evidence for recommendations were determined according to American Academy of Neurology study classification, and no financial conflicts of interest were declared by the authors.

Institute of Medicine

In 2011, the Institute of Medicine published a report on cognitive rehabilitation for traumatic brain injury that included a comprehensive review of the literature and recommendations. The report concluded that "current evidence provides limited support for the efficacy of CRT [cognitive rehabilitation therapy] interventions. The evidence varies in both the quality and volume of studies and therefore is not yet sufficient to develop definitive guidelines for health professionals on how to apply CRT in practice." The report recommended that standardization of clinical variables, intervention components, and outcome measures was necessary to improve the evidence base for this treatment. The Institute of Medicine also recommended future studies with larger sample sizes and more comprehensive sets of clinical variables and outcome measures.

National Institute of Health and Care Excellence (NICE)

- **COVID-19** – In 2021 (updated in 2024), NICE issued a rapid guideline on managing the long-term effects of COVID-19. The guideline recommends using a "multidisciplinary approach to guide rehabilitation, including physical, psychological and psychiatric aspects of management." Cognitive rehabilitation was not specifically addressed. Assessing the clinical effectiveness of "different service models of multimodality/ multidisciplinary post-COVID-19 syndrome rehabilitation in improving patient-reported outcomes (such as quality of life)" was listed as a key recommendation for research.
- **Dementia** – In 2018, NICE guidance on dementia management suggested: "Consider cognitive rehabilitation or occupational therapy to support functional ability in people living with mild to moderate dementia."
- **Stroke** - In 2013 (updated in 2023), NICE guidance on stroke rehabilitation recommends cognitive rehabilitation for visual neglect and memory and attention deficits that impact function. Interventions should focus on relevant functional tasks, e.g., errorless learning, and elaborative techniques (mnemonics, encoding strategies) for memory impairments. The guidance states that providers should 'Make special arrangements for people after stroke who have communication or cognitive needs (for example, by holding joint speech and language therapy and physiotherapy sessions for those with communication difficulties).'

The NICE guidance development is a transparent process that provides detailed information on the strength of recommendations and information on potential conflicts of interest for guideline committee members.

Veterans Administration/Department of Veterans Affairs (VA)

In 2009, the Veterans Administration/Department of Veterans Affairs published guidelines on the treatment of concussion and mild traumatic brain injury, which were updated in 2016, and most recently in 2021. These guidelines addressed cognitive rehabilitation in the setting of persistent symptoms. The 2021 guidelines stated:

- "We suggest that patients with symptoms attributed to mild traumatic brain injury [mTBI] who present with memory, attention, or executive function problems despite appropriate management of other contributing factors (e.g., sleep, pain, behavioral health, headache, disequilibrium) should be referred for a short trial of clinician-directed cognitive rehabilitation services." [Strength of recommendation: "weak for."]
- "We suggest against the use of self-administered computer training programs for the cognitive rehabilitation of patients with symptoms attributed to mTBI." [Strength of recommendation: "weak against."]

A 2019 Veterans Administration/Department of Defense practice guideline on the management of stroke rehabilitation found "insufficient evidence to recommend for or against the use of any specific cognitive rehabilitation methodology or pharmacotherapy to improve cognitive outcomes" and noted "there has been very little advancement in the evidence regarding the use of specific cognitive rehabilitation strategies or techniques to improve clinical outcomes following stroke."

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) updated the guideline (Version 2.2025) on Survivorship relating to cognitive function following cancer treatment. NCCN indicates that there is growing evidence that support the validity of patient-reported experience of cognitive dysfunction associated with cancer diagnosis and treatments. However, there is limited evidence to guide management of this condition. Patients who report cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment (i.e., depression, sleep disturbance, fatigue, delirium). Interventions may include neuropsychological evaluation, cognitive rehabilitation, psychotherapy, routine physical activity, or a trial of medications.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	97129	Therapeutic interventions that focus on cognitive function (eg, attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (eg, managing time or schedules, initiating, organizing, and sequencing tasks), direct (one-on-one) patient contact; initial 15 minutes

Codes	Number	Description
	97130	Therapeutic interventions that focus on cognitive function (eg, attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (eg, managing time or schedules, initiating, organizing, and sequencing tasks), direct (one-on-one) patient contact; each additional 15 minutes (List separately in addition to code for primary procedure)
HCPCS		
	S9056	Coma stimulation per diem
Type of Service	Therapy	
Place of Service	Inpatient/ Outpatient	

POLICY HISTORY

Date	Reason	Action
July 2025	Annual Review	Policy Renewed
May 2024	Annual Review	Policy Revised
May 2023	Annual Review	Policy Revised
August 2022	Annual Review	Policy Revised
August 2021	Annual Review	Policy Revised
August 2020	Annual Review	Policy Revised
August 2019	Annual Review	Policy Revised
August 2018	Annual Review	Policy Revised
August 2017	Annual Review	Policy Revised
August 2016	Annual Review	Policy Revised
September 2015	Annual Review	Policy Revised
October 2014	Annual Review	Policy Revised
October 2013	Annual Review	Policy Renewed

Date	Reason	Action
November 2012	Annual Review	Policy Renewed
November 2011	Annual Review	Policy Renewed
October 2010	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
 Medical Policy Analyst
 PO Box 9232
 Des Moines, IA 50306-9232

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