Educational Module 6

Cognitive Disorders Post ABI

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6.1 Remediation of Attention, Concentration & Information Processing Speed

Evaluating the efficacy of remediation or rehabilitation of attention deficits following a brain injury is complicated by a number of factors. First, ***there is no consensus regarding a definition of attention.*** Is it a general construct or does it reflect more specific sub-components or systems of functioning (e.g., sustained, divided, focused, selective, vigilance, speed of information processing, etc). Second, ***different researchers and clinicians will report using the same or similar tests to measure different aspects of attention.*** Third, ***a study may use the same outcome measures repeatedly, thereby confounding practice and treatment effects*** (e.g., PASAT performance improves significantly with repeated exposure to the test). Finally, ***studies may not consider and account for the rate of spontaneous recovery following brain injury*** (i.e. Would participants naturally show recovery of function in the absence of treatment?).

Comparing the efficacy of various remediation efforts is also complicated by cross-study variability in treatment duration (e.g. from 30 minutes once a day for 5 days to 5 hours, every day for 6 weeks). Severity of injury and time since injury may also fluctuate from study to study.

Cicerone et al. [1] reviewed 13 studies investigating the effectiveness of attentional retraining interventions during rehabilitation following traumatic brain injury and stroke. In 2005, five studies were added specific to the TBI population. **Cicerone et al.** [2] ***recommended strategy training for persons with TBI for improving deficits of attention.*** It should be noted, however, that ***there was insufficient evidence to distinguish the effectiveness of specific attention training during acute stage rehabilitation from improvements made from spontaneous recovery or from more general cognitive interventions*** [2]

According to ABIKUS Recommendations [3]

Cognitive Rehabilitation

All patients after moderate to severe ABI should be referred for neuropsychology, occupational therapy and speech language assessment to evaluate cognitive functioning. (ABIKUS C) (G32-p.21)

The treatment team should be multidisciplinary and is based on the individual's developing needs as determined by initial and ongoing assessment and goals. (ABIKUS C) (G33-p.21)

In order to facilitate/achieve generalization of skill/strategies to daily activities, rehabilitation should :

- *Focus on engaging in activities that are perceived as meaningful*
- *Include therapy interventions in the affected person's own environment and/or application to the person's own life*

(ABIKUS B) (G34-p.21)

Strategy training across all cognitive domains is recommended during postacute rehabilitation for persons with TBI (ABIKUS A, adapted from Cicerone et al. 2005) (G35-p.21)

Cognitive rehabilitation should include the use of periodic, random auditory alerting tones to improve sustained attention in subacute ABI/TBI. (ABIKUS A, adapted from Cicerone et al. 2005) (G36-p.22)

6.1.1 Pharmacological Interventions

6.1.1.1 Donepezil

Q1. What is the evidence for the use of a cholinesterase inhibitor in treatment of cognitive disorders following TBI?

Answer

1. There is level 1evidence, based on a single RCT, that Donepezil improves attention and short-term memory.

Discussion

The effectiveness of the ***cholinesterase inhibitor***, Donepezil, for improving cognitive functioning following brain injury was assessed in one study. **Zhang et al.** [4] conducted a randomized placebo controlled double-blind cross-over trial of 18 post acute TBI patients which demonstrated that ***donezpil significantly increased scores on tasks of sustained attention and short-term memory when compared to placebo*** and that these improved results were sustained after the wash-out period.

6.1.1.2 Methylphenidate

Q2. What is the evidence for the use of methylphenidate in the treatment of cognitive disorders post TBI?

Answer

1. There is conflicting evidence regarding the effectiveness of the administration of methylphenidate following brain injury for the improvement of cognitive functioning.

Discussion

Methylphenidate is a stimulant whose exact mechanism is unknown [5], although it is thought to act on the presynaptic nerve and ***acts to reduce the reuptake of serotonin and norephinephrine*** [6]. Methylphenidate has been extensively used as a treatment for attention deficit disorder, as well as narcolepsy [7].

Four randomized controlled trials examined the efficacy of methylphenidate as a treatment for the recovery of cognitive deficits post- brain injury. In a RCT examining the effects of methylphenidate, a psychostimulant on attention, **Whyte et al.** [8] indicated that ***speed of processing, attentiveness during individual work tasks and caregiver ratings of attention were all significantly improved with methylphenidate treatment***. No treatment related improvement was seen in divided or sustained attention or in susceptibility to distraction. Another RCT by **Plenger et al.** [9] also found that ***methylphenidate significantly improved attention***. **Speech et al.** [10] conducted a double blind placebo controlled trial evaluating the effects of the stimulant medication methylphenidate following closed head injury. In contrast to the results noted by Whyte et al. [8] and Plenger et al. [9], methylphenidate ***did not demonstrate significant differences compared to placebo on measures of attention, information processing speed, or learning***. **Kim et al.** [6] examined the effects of a single-dose treatment of methylphenidate and, although ***a trend was found in favour of improved working and visuospatial memory for the treatment group***, these results did not reach significance.

Study Snapshot

Whyte J, Hart T, Vaccaro M, Grieb-Neff P, Risser A et al. Effects of methylphenidate on attention deficits after traumatic brain injury: A multidimensional, randomized, controlled trial. *Brain Injury* 2004:83(6):401-420.

- 34 individuals who had sustained a moderate to severe TBI were selected for participation in the following randomized cross over study.
- All were given either methylphenidate (.3mg/kg) or placebo twice daily.
- Study results found methylphenidate had positive effects on speed of information processing ($p<0.001$) performance speed work task attentiveness ($p=0.01$), and caregiver ratings of attention ($p=0.01$).
- No treatment-related improvements observed in susceptibility to distraction, and divided or sustained attention.

According to ABIKUS Recommendations [3]:

Medication for Arousal and Attention

Methylphenidate (0.25-0.30 mg/kg bid) is recommended in adults to enhance attentional function in the adult population. Methylphenidate (0.25-0.30 mg/kg bid) is also recommended to enhance the speed of cognitive processing, although only one study provides evidence to support a change in speed in a naturalistic task. (ABIKUS A, adapted from GPT, I, p.1482) (G44-p.23)

6.1.2 Drill & Practice

Q3. What evidence is there for drill and practice in the form of structured training programs on attention post ABI?

Answer

1. There is Level 2 evidence to suggest that specific structured training programs designed to improve attention are ineffective or at best equivocal in their effects on attention.

Discussion

The following studies examined the influence of “drill & practice” exercises (either computerized and/or paper-and-pencil) on attentional functioning.

Novack et al. [11] performed an RCT of severe TBI participants in acute rehabilitation and found no difference between two treatment groups *“a focused group consisting of sequential, hierarchical interventions directed at specific attention mechanisms and an unstructured intervention* consisting of nonsequential, nonhierarchical activities requiring memory or reasoning abilities”. ***No differences were found between groups in attentional, functional and/or cognitive skills assessed, although post-intervention improvement of all subjects was demonstrated as compared to pre-intervention.*** It should be noted that this could reflect spontaneous recovery, as a “no-treatment”, control group was not included.

Similarly, **Park et al.** [12] examined whether “attention processing training (APT)” had a beneficial effect on attention measures (PASAT, Consonant Trigrams) in a severe TBI group (tested pre and post training approximately 7 months apart). They compared their results to a “convenience” sample of controls, given the same measures one-week apart without training. Results suggested that ***APT did not have a significantly beneficial effect as performance improved on all measures across both groups*** (indicating practice effects and possibly spontaneous recovery).

Ponsford and Kinsella [13]***,*** using a multiple-baseline-across-subject design, looked at the performance of severe TBI participants and a matched control sample on computerized tests of attention and measures of cognitive functioning following training. Training consisted of: (1) Phase I: 30 minutes a day for 3 weeks using computer mediated tasks of visual reaction time, visual search and selective attention and (2) Phase II: same as phase I but with feedback and reinforcement provided by the therapist***. Results indicated no effect of training with or without feedback /reinforcement and all participants improved across staggered baseline periods suggesting spontaneous recovery.***

Gansler and McCaffry [14] using an A-B-A design found ***no clinically significant effects on attention measures*** following an 8 week hierarchically ordered attention-remediation program (based on Posner’s 4 component model).

Niemann et al. [15] examined computer-assisted attention retraining in 26 moderate to severe TBI participants. They used a multiple baseline pre-test post-test comparison of two groups: attention group (treatment) and a memory group (control). ***The authors reported that the results supported attention training (better performance). However it is unclear whether the effect was a result of practice (e.g., measures were given 11 times) or specific to one particular test.*** That is, they did not indicate whether similar results occurred with repeated testing in the control group and whether each of the 6 measures increased at the same or similar rates.

6.1.3 Dual-Task Training

Q4. What is the evidence for dual-task training on speed of processing post ABI?

Answer

1. Based on a single RCT there is Level 2 evidence that dual-task training on speed of processing is effective.

Discussion

The following studies examined the effect of "dual-task" training on speed of processing.

Stablum et al. [16] compared two patient groups (those suffering from a closed head injury (CHI) and those who experienced an aneurysm of the anterior communicating artery (ACoA) and matched controls) on performance on a dual-task paradigm and neuropsychological tests. ***Results suggested that CHI and ACoA patients had significant difficulty compared to matched controls on dual-task reaction time measure and specific measures of executive functioning (e.g., WCST and PASAT)*** and compared to their own performance on a single-task reaction time measures (non-significant differences between groups on this latter measure). ***With training, however, performance improved to levels similar to matched control subjects and was maintained at follow-up 3 months later.*** However, what remains unclear is whether training generalized to functional gains or whether it remained specific to this specific dual-task.

Fasotti et al. [17] randomly assigned 22 severe TBI patients undergoing rehabilitation to either Time Pressure Management (TPM) training (treatment group, N=12) or to a concentration group (control, N=10). Patients were pre-selected for inclusion in this study if they demonstrated slowed processing speed (as measured by 3 tests). TPM consists of a series of cognitive strategies to compensate for reduced processing speed. There are 3 main stages: increased self-awareness of errors and deficits, acceptance and acquisition of TPM cognitive strategies (4 steps), and strategy application and maintenance in increasingly more demanding/distracting situations. The concentration-training group consisted of 4 generic suggestions (e.g., focus, don't get distracted, etc). Groups were compared on pre-training, post-training and follow-up on task performance (information from a video recording) and results indicated that there were ***no significant differences between groups (both improved task performance), although the TPM made more gains and appeared to generalize to positive effects other measures.***

6.2 Remediation of Learning and Memory Deficits

6.2.1 Treatment of Learning and Memory Deficits

Memory impairment is one of the most common symptoms following brain injury and it is estimated that time and cost of care would be reduced if effective medical treatments were found to improve memory [18]

Q5. Describe the two major approaches to learning and memory deficits post ABI.

Answer

1. Restoration: remediation of memory deficits.
2. Compensation: circumventing the difficulty which arises because of the memory deficit.

Q6. What are different examples of these two approaches?

Answer

Restoration: remediation of memory deficits.

- External compensatory aids including computers, pagers and notebooks
- Individualized remediation programs
- Family/social support
- Enviornmental adaptations
- Didactic lessons and homework

Compensation: circumventing the difficulty which arise because of the memory deficit.

- Rehearsal
- Organizational strategies
- Visual imagery
- Verbal labeling
- Use of mnemonics
- Implicit memory tasks

Discussion

When evaluating intervention strategies to improve memory performance following brain injury, the literature indicates that there are two main approaches to rehabilitation: restoration or compensation. **Compensation** includes ***"training strategies or techniques that aim to circumvent any difficulty that arises as a result of the memory impairment."*** Compensatory techniques include internal aids, which are "mnemonic strategies that restructure information that is to be learned." Various interventions have focused on: **1) Remediation** of memory deficits in individuals with TBI, including external compensatory aids (computers, pagers, and notebooks), individualized remediation programs, family/social support and environmental adaptations, didactic lessons and homework; **2) Compensatory Strategies** including rehearsal, organizational strategies, visual imagery, verbal labeling, and use of mnemonics, as well as implicit memory tasks.

Cicerone et al. [1] reviewed 42 studies examining the effectiveness of various interventions to improve memory impairment following stroke and TBI. It should be noted that studies were not included in our review if the population did not comprise of more than 50% brain-injured patients, or if the sample size (n) was less than 3. For this reason, only those studies dealing with moderate-to-severe brain-injured individuals are included in our review. Thirteen additional studies were added to the review in 2005 [2].

In an updated review by **Cappa et al.** [19] ***strategies used to improve memory deficits without the use of electronic, external aids were judged to be "possibly effective." Specific learning strategies (e.g. errorless learning) were found to be "probably effective" depending upon the task used, the type of memory involved and the severity of impairment.***

Several studies were identified examining interventions to improve learning and memory following acquired brain injury. Studies were categorized into the following groupings: external aids used to enhance memory, internal strategies used during learning to enhance recall, and memory intervention programs consisting of a number of sessions.

According to ABIKUS Recommendations [3]

Learning and Memory

Cognitive rehabilitation should include the use of self instructional training/internal training (e.g. self cueing, self talk). (ABIKUS A) (G37-p.22)

Cognitive rehabilitation should include the use of errorless learning for task specific learning for people with severe memory impairment. (ABIKUS B) (G38-p.22)

6.2.2 External Aids

Q7. What evidence is there for external memory aids?

Answer

1. There is conflicting evidence as to whether external memory aides are an effective strategy for memory-impaired individuals.

Discussion

External aids assist memory by use of external methods of recording and accessing information. In an updated review by Cappa et al. [19], the use of external, electronic assistive devices were assessed as "probably effective." Fourteen studies examined how external aids could be used to enhance memory following brain injury.

Wright et al. [20] examined the effect of two pocket computer systems containing three memory aides: appointment diary, notebook, and a to-do-list with a group of 12 ABI participants (9 TBI, 2 ABI). The type of pocket computer was counterbalanced and participants used each one for 8 weeks**. No significant difference in use was found between type of pocket computer (they differed in terms of text entry – physical keyboard or touch- screen keyboard)**, and the majority (83%) used the three aids. Those participants who had previously used a memory aid made significantly more diary entries compared to those who had not previously used a memory aid. Severity of injury as well as level of cognitive function was not reported in this study. In another study by Wright et al. [21], findings were similar (i.e. no differences between computer systems in terms of use of memory aids).

Wilson et al. [22] evaluated the efficacy of NeuroPage, a portable paging system, in reducing everyday memory problems in 15 ABI participants (10 TBI, 5 ABI). Using an A-B-A design, results indicated that ***all subjects significantly benefited from using the NeuroPage system and that following 12 weeks of use, performance remained at improved levels compared to baseline for another 3 weeks.*** **Wilson et al.** [23] conducted a randomized controlled cross-over trial with 143 memory impaired patients, many – how many having sustained a TBI. The objective for this study was to evaluate a paging system designed to improve independence in people with memory problems as well as to reduce deficits in executive function. ***Results demonstrated that the pager system significantly increased patients' ability to carry out daily tasks, and successful task achievement was more efficient after the pager intervention was introduced***.

Hart et al. [24] ***used hand-held recorders to remind moderate-to-severely impaired patients of their therapy goals (within subject design).*** Six individual goals were determined and half were recorded onto a hand-held organizer with an alarm preprogrammed to review the goals 3 times a day throughout the week. The other half of the goals were not recorded but were summarized at the weekly clinical management meetings. ***Goals were correctly recalled when using the hand held recorder compared to when goals were reviewed.*** It should be noted that the study examined only if the goals could be elicited during recall (either free recall or cued) and did not examine whether the subjects actually followed through with their goals.

Burke et al. [25] used a complex computerized tracking system (patient locater and reminder system – PLAM) to remind and direct 5 patients on an acute rehabilitation unit to their next therapy appointment. ***The electronic tracking system prompted patients 10 minutes in advance of their appointments and continued to do so until the patient started moving toward the therapy room.*** If patients were going in the wrong direction, the system would prompt them on how to get to the appointment and would offer positive reinforcement as the patient made their way to the therapy room. Using a case series design, baseline data was gathered for a week and included the number of staff prompts needed to get the person to scheduled therapy and the time the person arrived at the therapy. Once the patients were introduced to the PLAM system, data was collected for a 3-day period. ***Results indicated that the subjects arrived earlier to their appointments and required fewer prompts (i.e. the number of sessions that did not require prompting increased from 7% to 44%).***

Using a memory notebook as the external memory aid, **Schmitter-Edgecombe et al.** [26] ***assigned 8 individuals with severe closed-head-injury and memory deficits into either a notebook-training group or an interpersonal support group (control).*** Groups were matched on a number of demographic variables. Outcome measures included both performance on memory tests as well as observation and responses to a questionnaire on everyday memory failures. Both groups received 2, 1-hour sessions per week for 8 weeks (16 sessions***). Results indicated that, on cognitive measures of memory functioning, there was no difference between groups***. However, on observed everyday memory failures (questionnaire), performance improved (i.e., less failures) following treatment, although performance was not maintained at 6-month follow-up.

In a randomized controlled trial, **Watanabe et al.** [27] ***examined whether use of a calendar would enhance orientation following an acquired brain injury. Results indicated that the presence of a calendar did not enhance performance on a temporal orientation test*** (date and time). It is difficult to judge the outcome of this study as no scores were reported for either the control or treatment group, and it is not clear whether post-traumatic amnesia, and/or severity of injury had an impact on performance.

Ownsworth and McFarland [28] evaluated two different training approaches in the use a diary to compensate for memory problems. ***They randomly assigned 20 ABI volunteers (15 TBI; 5 ABI) to either a Self-Instructional Training (SIT) approach or to a task-specific learning approach.*** The Diary-SIT approach trains compensation using higher cognitive skills of self-regulation and self-awareness. That is, participants where taught to question themselves with the following script (WSCT): What are you going to do? Select strategies; Try it out; Check how it's working. ***By using this training approach, the researchers speculated that it provides direct, internal feedback, which can generalize to other situations involving memory. In contrast the Diary-Only approach taught subjects how to use the diary.*** Results indicated that those in the Diary-SIT group made consistently more diary entries, reported a reduction in everyday memory problems and made more positive ratings on treatment efficacy compared to the Diary-Only group.

Cicerone et al. [1] ***recommended that the use of memory notebooks or other external aids "may be considered for persons with moderate to severe memory impairments after TBI [and] should directly apply to functional activities, rather than as an attempt to improve memory function per se."***

6.2.3 Internal Aids

Q8. What is the evidence for internal memory aids?

Answer

1. There is Level 2 evidence (from several studies) that internal strategies appear to be an effective aid in improving recall performance.
2. There is Level 3 evidence from several case-control studies that internal strategies appear to assist in improving recall performance.

Discussion

Four randomized controlled trials, seven prospective controlled trials (plus one follow up study) and three single group interventions examined the effect of strategy use on memory following brain injury.

Twum and Parente [29] randomly assigned 60 TBI patients into one of 4 groups (one control and three mnemonic strategy groups) counterbalanced. The researchers demonstrated ***improved performance for subjects who were taught a strategy (either verbal labeling or visual imagery) while learning paired-associations. Treatment groups showed greater efficiency in learning and greater delayed recall information.***

Ryan and Ruff [30] ***used mnemonic strategies, including visual imagery*** in a memory group and found that these strategies ***enhanced performance for mildly impaired subjects only***

(severely impaired group showed non-significant findings between control and treatment groups).

Goldstein et al. [31] and **Malec et al.** [32] evaluated a visual-imagery technique ("Ridicuously Imaged Story" technique (RIS)) in training severely brain injured individuals to learn and recall lengthy word lists. Goldstein et al. [31] evaluated whether there were differences between a computerized and non-computerized version of RIS and another visual imagery technique (Pictorial Imagery). Results indicated that although the computerized versions resulted in a slightly better performance on learning trials, the difference was non-significant. **Malec et al.** [32] used the RIS technique to examine the predictors of memory training success and found that ***the "better subjects did at tasks similar to those which they were trained, the better their learning and capacity to generalize."***

By using the various visual imagery techniques to aid learning and recall, researchers have demonstrated that increasing the saliency of features encoded, results in an increase in the amount recalled. **Milders et al.** [33] ***examined performance on a name learning task by increasing the meaningfulness of people's names with various strategies*** (e.g. when learning a new name-face association try to think of an occupation or object with the same name or a famous person with a similar name etc). When subjects (13 severely TBI vs. 13 matched controls) were tested on 3 different memory tasks, ***results indicated a significant difference following training, more so for the control group than the TBI group***. Also, learning procedures were more effective on one task (where subjects were required to learn the name-occupation-and town) compared to the other two tasks (famous-faces or name learning), which supports Malec et al. [32] findings of ***generalization when tasks are similar***. **Goldstein et al.** [34] found that semantic processing aids recognition of to-be-recalled words compared to processing words at a more perceptual level in both closed head injury patients and control subjects (of course the degree of facilitation is reduced in the TBI group compared to controls).

Zencius et al. [35] examined the differential effects of various strategies on recall of information. Six TBI patients were asked to find two jobs from the help wanted column of a newspaper extracting 3 pieces of information for each job. They were asked either to learn the information for later recall using one of the following strategies: verbal rehearsal, written rehearsal, acronym formation or notebook logging. All strategies resulted in improved performance (number of information correctly recalled) with the exception of written rehearsal (performance similar to baseline). ***Notebook logging resulted in the best performance.***

Berg et al. [36] demonstrated that ***severely brain injured patients demonstrated improved effects on objective measures of memory at 4 months following training in a strategy-use group compared to a pseudo-treatment and a no treatment control group.*** In the strategy group, individuals were taught general cognitive principles of memory functioning and aids (i.e., internal and external strategies were taught and practiced). In contrast, the pseudo-treatment group practiced memory games and tasks with no explanation. In a 4 year follow up study Milders et al. [37] results demonstrated that the effects at 4 months were no longer evident at 4 years (all groups were equivalent).

How individuals learn (i.e., encode) information will determine to a large extent what is later recalled. **Twum and Parente** [29] ***demonstrated that if an active strategy (either verbal labeling for visual information or visual imagery for verbal information) is taught to individuals while learning the paired associations, learning and recall is enhanced*** (i.e., fewer trials needed to reach criterion during learning and improved recall following a delay).

Tailby and Haslam [38] also examined how learning can improve or limit later recall of information. They had 24 ABI subjects matched on basis of age, gender, premorbid and current intellectual status divided into 3 groups based on performance of verbal memory (mild, moderate & severe). Each group (n=8) was randomly assigned to one of 3 learning conditions: errorless learning, self-generated; errorless learning, experimenter generated; and errorful learning. ***Results showed that regardless of severity level, subject recalled more information in the errorless learning conditions (with self-generated superior to experimenter generated) than in the errorful learning condition.***

Constantinidou and Neils [39] examined the effects of stimulus modality on verbal learning of patients with moderate-to-severe closed head injury and a matched control group***. Results indicated that when information is presented visually (with and/or without auditory presentation of names) more information is learned than when information is presented within the auditory modality alone.*** As expected, patients learn new information at a significantly slower rate compared to controls.

It is generally thought that while patients are experiencing post-traumatic amnesia (PTA), they are not able to learn and retain new information, and as a result, cognitive rehabilitation is usually postponed until PTA has resolved. This tends to be true if using tasks of explicit or declarative learning and recall. Two studies were reviewed that reported that PTA patients were capable of learning and retaining new information when task demands were dependent on implicit/procedural learning. **Glisky and Delaney** [40] evaluated implicit memory (priming using a stem completion task) and the use of vanishing cues when learning semantic information in a small number of TBI patients (n=8 & 4) who were still experiencing PTA and a matched control group. Findings revealed that learning and recall of information (once PTA has resolved) had occurred, albeit at reduced levels compared to controls**. Ewert et al.** [41] also demonstrated procedural learning and retention in a group of 16 severely closed head injured participants and matched controls.

6.2.4 Memory Programs

Q9. What is the evidence for memory-retraining programs post ABI?

Answer

1. There is Level 2 evidence, based on a single RCT, that memory-retraining programs appear effective, particularly for functional recovery although performance on specific tests of memory may or may not change.

Discussion

Ryan and Ruff [30] ***randomly assigned 20 severely brain injured individuals***, matched for age, gender, education, and time since injury, ***to either a memory retraining group or a psychosocial group (control).*** Treatment lasted for 6 weeks (4 days per week, 5.5 hours per day for each group. Initially no differences were observed between groups on neuropsychological measures of memory. When groups were subdivided based on neurocognitive severity (mild vs severe), ***results indicated that the mildly impaired group benefited more than the severely impaired group from memory retraining.***

Freeman et al. [42] conducted a ***matched-controlled treatment outcome study to evaluate executive and compensatory memory retraining in traumatic brain injured patients.*** 12 patients were included in this study; six who received remediation treatment, which involved repeated presentation of various paragraphs, and six who received no treatment. A significant difference was found between the treatment group and the control group's post-training measures with the experimental group improving considerably more than the control group. ***Results suggest that memory remediation is effective for brain-injured patients with memory impairments.***

Evans and Wilson [43] ***examined the effects of a memory group that met weekly for 11 months*** (2 hours a week for approximately 48 weeks). Family and individuals reported an increase in using memory aides and strategies at 7 months and at 11 months compared to baseline (no objective measures were given and it is unclear if beneficial). ***Scores on neuropsychological measures of memory did not change over time.*** A main drawback of this study is the researchers' failure to describe the nature and content of the memory program.

Quemada et al. [44] ***examined memory rehabilitation following severe TBI in 12 individuals.*** The program ran for 6 months (50 minute sessions 5 days a week for 5 months and then 3 days a week for one month) and followed a specified format utilizing behavioural compensation techniques, mnemonic strategies, environmental adaptations, external and internal aides. ***Results indicated little improvement in standard measures of memory functioning, although patients and family members report meaningful functional gains*** (self-report and observed behaviour in everyday functioning).

Hux et al. [45] ***examined the effect of training frequency on face-name recall.*** The study included 7 TBI patients with demonstrated memory impairment in a modified multiple-baseline design utilizing 3 training phases (daily sessions, twice a week session and 5 times a day). The phases were counterbalanced, thereby eliminating any order effect. Daily sessions as well as twice a week sessions were found to be more effective than sessions that occurred 5 times a day. ***Mnemonics and visual imagery strategies were effective for 4 of the 7 participants regardless of frequency of intervention sessions.***

6.2.5 Cranial Electrotherapy Stimulation and Memory

Q10. What is the evidence for cranial electrostimulation in improving memory?

Answer

1. There is Level 1 evidence, from one RCT, that cranial electrotherapy stimulation did not help to improve memory and recall following brain injury.

Discussion

Cranial electrotherapy stimulation (CES) is the application of less than 1 mA of electric current to the cranium. This application has been used to treat a variety of disorders, including treatment of withdrawal of patients with substance abuse [46]. The effect of CES for the improvement of memory following brain injury was investigated.

Michals et al. [46] ***studied cranial electrotherapy stimulation and its effect on post-traumatic memory impairment in clinical care patients with closed head injury.*** Patients received CES or sham CES treatments for 40 minutes daily over a period of four weeks. The group receiving CES treatment did not improve in their memory performance, nor did their immediate or delayed recall improve. Further, with retesting, both the CES and the sham CES group showed a similarly significant trend with no group performing any better than the other. ***These results suggest that CES stimulation in brain-injured patients does not improve memory functioning.***

6.2.6 Pharmacological Intervention

According to ABIKUS Recommendations (2007)[49]:

Medication for Management of Memory

Donepezil (5-10 mg/day) is recommended to enhance aspects of memory function for patients with moderate to severe TBI in subacute and chronic periods of recovery (ABIKUS B, adapted from GPT, 1, p. 1482) (G39-p.22)

Methylphenidate in a dose of 0.30 mg/kg bid may be considered as an option to enhance learning and memory in persons who are within a few months of brain injury onset when other strategies are ineffective (ABIKUS B, adapted from GPT, I, p.1483) (G40-p.22)

6.2.6.1 Amantadine

Q11. What is the evidence for amantadine in treating memory deficits post ABI?

Answer

1. There is Level 4 evidence that amantadine does not help to improve learning and memory deficits based on the conclusions of a single group intervention study.

Discussion

Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist and is currently used as an antiviral agent used as a prophylaxis for influenza A, for the treatment of neurological diseases such as Parkinson's Disease and in the treatment of neuroleptic side-effects such as dystonia, akinthesia and neuroleptic malignant syndrome [47]. It is also thought to work pre- and post-synaptically by increasing the amount of dopamine [5].

One study was identified that investigated the effectiveness of amantadine as a treatment for the remediation of learning and memory deficits. **Kraus et al.** [48] demonstrated that the administration of amantadine over a 12-week treatment period does not improve measures of memory deficits or attention.

6.2.6.2 Donepezil

Q12. What is the evidence for the use of a cholinesterase inhibitor in treatment of attention disorders following TBI?

Answer

1. There is level 1 evidence, based on a single RCT, that donepezil improves attention and short-term memory.

Discussion

Zhang et al. (2004) conducted a randomized placebo controlled double-blind cross-over trial of 18 post acute TBI patients which ***demonstrated that donezpil significantly increased scores on tasks of sustained attention and short-term memory*** when compared to placebo and that these improved results were sustained after the wash-out period, suggesting a carry over affect of the medication.

Study Snapshot

Zhang L, Plotkin RC, Want G, Sandel E, Lee S. Cholinergic augmentation with donepezil enhances recovery in short-term memory and sustained attention after traumatic brain injury. *Arch Phys Med Rehabil* 2004; 85:1050-1055.

- 18 patients who had sustained a traumatic brain injury and were 2 to 24 months post injury participated in this randomized control cross over study
- Participants were given either donezpil or placebo for 10 weeks then following a 4 week washout period, they began the second phase of the study.
- Intragroup comparisons indicate while on the donezpil participants showed significant improvement on the Auditory Immediate Index (AII), the Visual Immediate Index (VII) and the Paced Auditory Serial Addition Test (PASAT).
- Intergroup comparison results of the AII, VII and the PASAT showed the donepezil group improved significantly compared to the placebo group.

6.2.7 Summary of Learning and Memory Post ABI

Not all patients respond equally to all intervention strategies and no study in the current review indicated whether severity of memory impairment (or memory profile) interacts with a particular external memory aid. Technology has increased the availability of external aids, although some seem more feasible to use than others (e.g., cell phones or hand-held recorders). Unfortunately, the studies reviewed did not specify the length of time subjects required to master compensatory strategies nor the nature of the long-term effects, if any.

Most studies examined only tasks of word list recall and paired-associate learning suggesting that the mnemonic strategies reviewed may not generalize to other types of information (particularly real-world or functional information outside the laboratory). ***Errorless learning appears to be one procedure that can be used to enhance learning conditions.***

One study highlighted the difference between severity of impairment and ability to benefit from internal strategies.

Frequency of intervention has an impact on learning and retention, although the exact parameters of this are unclear at the present time. ***The optimal duration of a program is also open for speculation.*** No studies reviewed examined the number of sessions required for memory groups to be effective and only one study evaluated a difference in effectiveness between mild and severely impaired individuals after sessions.

Pharmacologic interventions do not appear to be overly effective in improving learning and memory deficits, with perhaps the exception of anti-cholinergic esterase inhibitors.

6.3 Remediation of Executive Functioning

Executive functions refer to higher-level cognitive functions that are primarily mediated by the frontal lobes. These functions include insight, awareness, judgment, planning, organization, problem solving, multi-tasking and working memory [50]. Executive deficits are particularly relevant following traumatic brain injury from both a pathophysiologic as well as a psychosocial perspective. The frontal lobes tend to be one of the brain areas most likely to be injured following trauma [51]. ***Frequently bilateral frontal lobe injury occurs following TBI*** in contrast to typical unilateral insults following vascular injury. ***Not only direct contusion to the frontal and temporal lobes but also diffuse axonal injury sustained as a result of TBI affect executive functioning.*** TBI patients often present with cognitive and behavioural deficits in the presence of little physical impairment.

Cicerone et al. [1] reviewed 14 studies dealing with executive functioning and problem-solving Only 3 of the identified studies were classified as a randomized controlled trial or non-randomized cohort study.

In an updated review**, Cicerone et al.** [2] identified 9 additional studies. Some of these studies were not included in our review as they dealt with mild severity of injury. Based on the results of the studies in their review, Cicerone et al. (2000) ***recommended, "training of formal problem-solving strategies and their application to everyday situations and functional activities".*** Executive function deficits are particularly relevant to brain injury survivors who tend to be younger (average age less than 40) and who often desire to re-integrate back into pre-injury life roles. Patients with primarily executive function deficits may have the capacity to be independent for basic activities of daily living where actions tend to be more ingrained and one-dimensional.

However, ***instrumental activities of daily living such as banking, scheduling and household activities require intact executive functions due to the increased cognitive complexity and variability of the tasks.*** Of particular importance are the advanced tasks such as return to driving and competitive employment which are of increased relevance to the younger age demographic associated with TBI [52].

Within the typical medical and rehabilitation settings, ***executive function deficits themselves are difficult to identify and evaluate since there is a tendency to focus on other cognitive functions such as memory and attention.*** The importance of evaluating effective interventions for treating executive dysfunction following brain injury is apparent since impairment can ultimately hinder successful community re-integration.

According to ABIKUS Recommendations [3]

Executive Functions

Use of metacognitive strategy training (e.g. goal/plan/do/review, goal management training) is recommended for people with executive dysfunction (ABIKUS A) (G41-p.22)

The following interventions are not recommended due to demonstrated lack of efficacy:

- *Sole reliance on repeated exposure and practice on computer based tasks with some involvement by a therapist*

- *Specific structured attention programs using drill and practice (ABIKUS A) (G42-p.22)*

6.3.1 Group Interventions

Q13. What evidence is there supporting group interventions for executive dysfunction post ABI?

Answer

1. There is conflicting evidence supporting the use of group-based interventions to treat executive dysfunction post ABI.

Discussion

Although executive function deficits are a common and important impairment post brain injury, there is little overall research directly addressing the impact of rehabilitation on executive function. However, community integration is highly related to executive function and it is possible that programs and interventions aimed at improving community re-integration may in fact be focusing efforts on instrumental activities of daily living for which intact executive functions are required.

In an RCT conducted by **Ownsworth et al.** [53], subjects were randomly assigned to a diary only (DO - n=10) group or a diary and self-instructional training (DSIT-n=10) group. The DO group participated in a 6 week "Bottom-Up" approach program that emphasized the development of functional skills using compensation based, on task,-specific learning. The DSIT group participated in a 10 week "Top-Down" approach program that emphasized the capacity for self-regulation and self-awareness using "Self Instructional Training." The comparison group (n=31), individuals who had not sustained a TBI, completed the self-report memory questionnaires. Results indicate ***no significant differences on the performance self-ratings, satisfaction self-ratings, relatives' performance ratings, and relatives' satisfaction ratings (p>0.05) for the intervention group. The satisfaction self ratings between pre and post assessment, indicated an improvement after each intervention*** (individual p<0.001; group p<0.025; combined p<0.01). At follow-up an improvement in self-rated satisfaction was noted for the group and combined interventions only (p<0.01). Results from the CPOM indicate that there were no significant differences when looking at the scores from the group intervention pre to post comparison (p<0.028). Significant improvement was noted when looking at the scores for the individual and combined interventions (p<0.01 and p<0.025 respectively). Pre assessment and follow-up assessment for the relatives' ratings of performance was significant for all three interventions (individual p<0.01; group p<0.01; combined p<0.025). Relatives' ratings of satisfaction (pre and post) found a significant improvement for the individual (p<0.025) and combined (p<0.01) interventions but not for the group intervention (p<0.117). A look at the psychosocial outcomes for each intervention group showed few significant differences.

Ownsworth et al. [54] studied the effect of group therapy aimed at improving self regulation skills as well as psychosocial functioning for brain injury survivors greater than 1 year post injury. Self regulation was evaluated using the self regulation skills interview which examines how brain injury survivors would handle self identified difficulties [54]. ***Both self regulation abilities and psychosocial functioning improved following the treatment intervention and improved performance was maintained at 6 month follow up.***

6.3.2 Goal Management Training

Q14. What is the evidence for goal management training of executive functioning deficits post ABI?

Answer

1. There is Level 2 evidence, based on a single RCT, that goal management training is effective for improving paper and pencil everyday tasks and meal preparation skills for persons with an ABI.
2. There is Level 4 evidence, based on a single group intervention, that a goal planning in the form of a leisure activities is effective for achieving identified goals following injury.

Discussion

With cognitive rehabilitation, much of therapy is patient goal directed with both long and short term goals often identified [55]. The ability to manage goals is often emphasized as a component of brain injury community reintegration programs and is integral in the completion of instrumental activities of daily living.

Levine et al. [56] completed a RCT comparing a group of patients taking goal management training strategies to a control group who were exposed to only motor skills training***. The treatment group improved on paper and pencil everyday tasks as well as meal preparation***, which the authors used as an example of task heavily reliant on self-regulation.

Walker et al. [57] conducted an alternative goal planning, cognitive rehabilitation program focusing on the development and achievement of goals following brain injury. This single group intervention involved three phases: (1) nine-months of planning and fund-raising for an outdoor adventure course; (2) a nine-day outdoor course; and (3) four-months following the course, the participants focused on goal achievement and problem-solving skills***. More than 80% of the identified goals of participants were achieved. No significant pre- and post-treatment differences were noted on psychological measures***: Depression, Anxiety Stress Scales (DASS), the General Well-Being Schedule (GWB), and the European Brain Injury Questionnaire (EBIQ). This program demonstrated a unique and challenging, community-based intervention for group goal management following brain injury.

6.3.3 Pharmacological Intervention

According to ABIKUS Recommendations [3]

Medication for Executive Dysfunction

Bromocriptine in a dose of 2.5 mg is recommended for use in enhancing aspects of executive functioning (e.g. divided attention/central executive functions) in patients with severe TBI (ABIKUS B, adapted from GPT, I, p.1482)

6.3.3.1 Amantadine

Q15. What is the evidence for amantidine improving executive functioning post ABI?

Answer

There is Level 4 evidence that amantadine does help to improve executive functioning based on the conclusions of a single group intervention.

Discussion

Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist and is currently used as an antiviral agent used as a prophylaxis for influenza A, for the treatment of neurological diseases such as Parkinson's Disease and in the treatment of neuroleptic side-effects such as dystonia, akinthesia and neuroleptic malignant syndrome [47]. ***It is thought to work pre- and post-synaptically by increasing the amount of dopamine*** [5].

Kraus et al. [48] demonstrated ***significant improvements in executive functioning*** following administration of amantadine over a 12-week treatment period. It should be noted that there were no significant differences noted for measures of memory deficits or attention.

Study Snapshot

Kraus MF, Smith GS, Butters M, Donnell AJ, Dixon E, Yilong C, Marion D. Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: A study using positron emission tomography (PET). *Brain Injury*, 2005; 19(7):471-479.

- Participants in the current study (n=22) were administered 400 mg of amantadine per day for a period of 12 weeks
- A series of neuropsychological tests were administered pre and post administration of the amantadine.
- Post treatment executive function scores significantly improved ($t(21) = -2.47$, $p=0.02$).
- Scores on the memory and attention domains showed no significant improvement.

6.3.3.2 Bromocriptine

Q16. What is the evidence for bromocriptine in treating executive functioning post ABI?

Answer

1. Based on a two RCTs there is conflicting evidence supporting the use of bromocriptine to enhance cognitive functioning.

Discussion

Bromocriptine is a dopaminergic agonist, which primarily affects D^2 receptors [58]. It has been suggested that dopamine is an important neurotransmitter for prefrontal or frontal lobe function [59].

In a randomized placebo controlled cross over study conducted by **Whyte et al.** [58] bromocritpine was administered to a group of individuals. Administration of bromocriptine was begun at 1.25mg/BID and increased to 5mg/BID. Individuals received the medication for 3 weeks before being titrated off the medication and placed on a placebo. Test results for all subjects indicate bromocriptine had little significant effect on their abilities to perform on a range of measures of attentional function. It was noted that several participants did experience moderate to severe drug effects and withdrew or were withdrawn from the study.

Study Snapshot

Whyte J, Vaccaro M, Grieb-Neff P, Hart T, Polansky M, Coslett HB. The effects of bromocriptine on attention deficits after traumatic brain injury: a placebo-controlled pilot study. *Am J Phys Med Rehabil.* 2008; 87:85-99.

- 12 participants were randomized to either the bromocriptine/placebo group (n=6) or the placebo/bromocriptine group (n=6)
- Participants received the bromocriptine or placebo for 4 weeks.
- Bromocriptine was started at 1.25 mg twice daily for 2 days, the dose was then increased to 2.25 mg twice daily for 3 days, then increased to 5 mg twice daily for the next 3 weeks. Following the 4th week, participants on bromocriptine were given the placebo and those in the placebo group were started on bromocriptine.
- Overall the administration of bromocriptine had little effect on the participants' abilities to perform on a range of measures of attentional function.

In an earlier study, **McDowell et al.** [59] examined the effects of low dose bromocriptine in a double-blinded, placebo-controlled cross-over design trial. Testing revealed that a low dose of bromocriptine (2.5 mg/daily) improved functioning on tests of executive control including a dual task, trailmaking test, the Stroop test, the Wisconsin Card-Sorting Test and the controlled oral word association test (FAS test). However, bromocriptine did not significantly influence working memory tasks.

Study Snapshot

McDowell S, Whyte J and D'Esposito M. Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. *Brain,* 1998; 121(6):1155-1164.

- In the following double blind cross over RCT, 24 participants were given 2.5 mg of bromocriptine or placebo.

- Participants were asked to complete the following cognitive tests: Stroop test, Spatial delayed-response task, Wisconsin Card Sorting Test (WCST), Verbal span task, Trailmaking test, and controlled oral word association test (FAS test).
- Bromocriptine was found to improve function on tasks that engage executive processes (dual task, trailmaking test, Stroop Test, verbal fluency and WCST) but it did not improve working memory (spatial delayed response task or reading span).

Although the McDowell et al. [59] study demonstrated benefits following administration of bromocriptine, there was only a single administration of bromocriptine or placebo and the dose was considerably lower than that given by Whyte et al. [58]. Spontaneous recovery may have been a factor leading to the improved abilities in individuals receiving a single dose (2.5mg daily) of the medication; however, study results did not answer this question. Results from Whyte et al. [58] noted that the placebo group demonstrated better (although not significant) trends in improvement on the various tasks administered.

6.3.4 Summary of Executive Function

The current studies support the notion that group cognitive interventions may be effective for improving executive functionThere is also some evidence that pharmacological intervention, amantadine, may be effective in improving executive function. Evidence supporting the use of bromocriptine is inconclusive. Ultimately, further research is required to determine which methods are most effective for improving executive function.

6.4 Cognitive Rehabilitation Strategies

Intervention for treatment of cognitive deficits post traumatic brain injury tend to be diverse with variability between the interventions themselves and the outcome measures used to document results. For the purposes of this section, interventions were included that either targeted multiple cognitive domains such as attention, memory, information processing speed, executive functions and visuoperceptual function or were non-specific with regards to intended outcome. For example, a general cognitive rehabilitation program would tend to document outcomes across multiple domains.

6.4.1 Cognitive Rehabilitation

Q17. What is the evidence for cognitive rehabilitation therapy post ABI?

Answer

1. There is conflicting evidence that a cognitive rehabilitation program focusing on memory strategies and selective attention will have a significant benefit relative to controls.
2. There is Level 4 evidence that general cognitive rehabilitation therapy post acquired brain injury is effective for improving cognition. Although there are variable strategies and protocols for cognitive rehabilitation, all comprehensive interventions appear to provide benefit.
3. There is Level 4 evidence that an outpatient day program is effective for assisting brain injury survivors in returning to competitive employment.

Discussion

Gordon et al. [60] conducted an extensive review of the traumatic brain injury rehabilitation literature and identified 13 studies dealing with rehabilitative treatments of cognitive deficits Gordon et al. [60] included studies based on several inclusion criteria: more than 20 participants with TBI and 20 controls, the sample was comprised of more than 75% adults, and more than 75% of the participants were individuals with TBI. **Fourteen studies** examining the effects of cognitive rehabilitation strategies are discussed here.

In a ***randomized controlled trial*** by **Dirette et al.** [61], although there were significant improvements on post intervention results for both intervention and control groups, there was ***no overall difference between groups when the experimental group was taught to use compensation strategies including verbalization, chunking and pacing.*** In this study, the authors did note that control participants spontaneously relied upon compensatory strategies, which may have accounted for improvement.

Rath et al. [62] completed an ***RCT comparing two cognitive rehabilitation therapies***: conventional (cognitive remediation and psychosocial components) versus an innovative rehabilitation approach focusing on emotional self regulation and clear thinking. Outcomes were measured across multiple domains of cognition including attention, memory, reasoning, psychosocial functioning, and problem solving measures. ***Significant changes comparing baseline to post intervention outcomes were seen for each group***, however, the improvements were different for the interventions. No between-group comparisons were made.

Neistadt [63] divided 45 patients into one of two groups: a ***remedial group who received individual training with parquetry block assembly, and an adaptive group who received functional skills training over a six-week period.*** Outcomes for the effect of treatment for constructional test performance revealed that the remedial group improved significantly more than the adaptive group on the Parquetry Block test. However, there were no significant differences on the WAIS-R Block Design subtest after treatment. Outcomes for the effect of treatment on functional test performance revealed a trend as predicted, although non-significant, toward the functional group improving more than the perceptual skills group. ***Training-specific learning appears to be an effective approach to rehabilitation as demonstrated by the treatment effect.***

Cicerone et al. [64] ***compared an intensive cognitive rehabilitation program to a standard rehabilitation program.*** This intensive program included individual and group therapy 4 days per week for 5 hours per day for a total of 16 weeks. The main outcome for this study was community integration post injury. The treatment group had a significantly better outcome compared to the control group. With regards to cognitive outcomes, analysis was not performed on the control group due to incomplete data; however, ***there was a significant improvement on post intervention composite neuropsychological scores for the treatment group who on average were better at two years post injury than at the start of the intervention.***

Harrington and Levandowski [65] demonstrated ***overall cognitive improvement in 18 TBI survivors following a two-year structured cognitive retraining program*** which consisted of 5 sequential instructional modules focusing on 1) orientation, attention/concentration and psycho-motor skills 2) perceptual cognitive processing 3) perceptual-cognitive integration 4) logical reasoning and problem solving and 5) a transitional community module. Pre- post comparisons demonstrated significant improvement on all elements of the Luria-Nebraska Neuropsychogical battery except for tactile functioning.

Brett and Laatsch [66] studied the effects of a cognitive rehabilitation therapy program for TBI survivors in a high school setting. The intervention included biweekly 40-minute sessions for a total of 20 weeks. ***Cognitive therapy focused on alertness, attention, concentration, perception and memory as well as problem solving. Only memory demonstrated a statistically significant improvement post intervention*** whereas general intellectual functioning, concentration and problem solving did not demonstrate significant improvement.

Rattok et al. [67] ***compared three cognitive rehabilitation programs which were similar in intensity, but varied in the emphasis of type of retraining format.*** This non-randomized controlled trial addressed cognitive retraining in the domains of attention, personal counseling, individual cognitive remediation and interpersonal communication exercises. ***All treatment mixes were equally effective with regards to level of vocational attainment.***

Ruff et al. [68] in an ***RCT compared an active treatment based group focusing on attention, spatial integration, memory and problem solving to a control group that focused on computer and video games, coping skills, health, discussion forum, independent living and art. Both groups improved significantly, however, the treatment group experienced relative gains on memory testing and selective attention, suggesting that focusing on these specific elements has the potential to improve them.***

Boman et al. [69] in a study of 10 individuals with mild or moderate TBI, after completing 1 hour of an individual cognitive training 3 times a week for 3 weeks, ***significant improvement was noted on the attention processing training test in sustained attention ($p<0.05$), selective attention ($p<0.05$), and alternating attention ($p<0.01$) pre to post training and at 3 month follow-up.*** Scores on the RBMT were also seen to have significantly increased at the 3 month follow-up compared to pre test scores ($p<0.05$). Changes on the Claeson-Dahl Memory test did not increase pre to post to 3 month follow-up.

Ben-Yishay et al. [70] reported a single group intervention of 101 patients with traumatic brain injury who ***entered into a comprehensive out patient day program*** consisting of two phases. At the end of the program, 84% were competitively employable, however over the intervening three years, this declined to only 50% remaining employed. Although no controls are available for this study, there is ***some evidence to support that a day program is effective for returning brain injury survivors to competitive employment.***

Prigatano et al. [71] in one of the earlier studies examining neuropsychological functioning found that a ***out-patient neuropsycholgical rehabilitation program provided significant benefit compared to a control group not receiving further rehabilitation.*** This comprehensive, intensive program emphasized increased awareness and acceptance of injury and residual deficits, intensive cognitive retraining and compensatory skills development. There was improvement in neuropsychological performance in the treatment group compared to the control group. Emotional distress was noted to substantially decrease in the treatment group.

Salazar et al. [72] in a RCT of 120 moderate to severe TBI patients ***studied the efficacy of an intensive, eight-week, in-patient cognitive rehabilitation program compared to a limited home rehabilitation program with weekly telephone contact from a psychiatric nurse.*** Overall there were ***no differences between groups*** with regards to return to work or fitness for duty at one-year. There were also no differences in cognitive, behavioral or quality of life outcomes.

Cicerone et al. [1] had concluded that comprehensive-holistic cognitive rehabilitation should be recommended as a practice guideline for patients with either a stroke or acquired brain injury. Since completion of this review, further quality studies have been published supporting a general cognitive therapy approach following acquired brain injury. In the studies by Dirette et al. [61], Rath et al. [62] and Cicerone et al. [64] comparisons of specific strategies using experimental techniques (randomized and non-randomized) are attempted. All groups demonstrated benefit from the interventions and in the studies by Rath et al. [62] and Cicerone et al. [64] there were overall trends to improvement for the experimental groups. The study by Salazar et al. [72] provides contradictory results to these other studies in that no benefit was demonstrated for an intensive in-patient rehabilitation program versus a limited home based rehabilitation program. This study was a RCT and challenges the trend of studies demonstrating the benefit of intensive cognitive rehabilitation programs.

Although there are differences in the delivery techniques of cognitive rehabilitation therapy, ***most studies when considering within-group comparisons demonstrated an overall improvement in cognitive abilities across multiple cognitive domains***. The majority of the studies included patients greater than one-year post injury, which would assist in controlling for the effects of spontaneous recovery. There are limitations in most studies in that typically a time series design is used with pre- and post-intervention testing where the subject acts as their own control. The primary limitation with regards to brain injury rehabilitation is time-dependent confounding. Two factors contribute to this including anticipated spontaneous recovery as well as the consideration of the practice/ learning effect of repeat neuropsychology testing which may lead to higher scores.

Analysis of findings from the current review as well as those from Cicerone et al. [2] and Gordon [60] all suggest that ***future studies need to control for patient characteristics (e.g., level of impairment needs to be clearly defined, not just severity of injury), spontaneous recovery and practice effects on outcome measures used.*** Studies should not just rely on psychometric tests but should consider functional outcome measures and long-term effects of treatment interventions should be monitored through follow-up.

6.4.2 Computer-Assisted Training

Q18. What is the evidence for computer assisted cognitive retraining post ABI?

Answer

1. There is Level 2 evidence that computer assisted cognitive retraining is not been an effective adjunct to the rehabilitation program, especially regarding attentional retraining following brain injury.

Discussion

A specific intervention for improving general cognitive functioning is computer- assisted training. The use of computer-assisted cognitive retraining has multiple potential benefits within the rehabilitation setting following brain injury. ***Computer retraining allows for flexibility in retraining procedures, increased individuality of therapy programs and also decreases the amount of direct time a therapist is with the patient. It also has the potential of continuing cognitive retraining within the community setting.*** Furthermore, as presented at the NIH Consensus Development Panel [73], computer-assisted strategies are used to improve neuropsychological processes, including attention, memory and executive skills. Eight studies were identified that used computer-assisted measures for cognitive rehabilitation following brain injury.

Dou et al. [74] in an ***RCT randomized participants to one of three groups:*** the computer assisted memory training group (CAMG-treatment - group 1) or the therapist administered memory training group (TAMG-treatment - group 2) with each receiving one month memory training or 3) the control group. Memory training was similar between the groups but they were delivered differently. The treatment groups received 20 training sessions with each running for 6 days per week and lasting approximately 45 minutes. The control group received no training. Sessions consisted of: training basic component memory skills in (1) the management of typical daily tasks utilizing/integrating the component memory skills, (2) customized programs and (3) skill consolidation as well as in the generalization of those skills in practice. ***Scores on the neurobehavioural cognitive status examination (NCSE) showed significant improvement in the TAMG and CAMG groups ($p<0.015$, $p<0.02$ respectively) compared to the control group. Results from the Rivermead behavioural memory test (Cantonese version) showed the CAMG improved significantly compared to the control group ($p<0.0001$). Those in the TAMG showed no significant improvement.***

Ruff et al. [75] evaluated the effect of computer assisted rehabilitation using the THINKable computer program which is a multi-media system that focuses on memory and attention retraining. Although this study was designed as a randomized controlled cross over design, due to the small number recruited (15), the groups were analyzed together in a pre-post intervention fashion***. Psychometric testing revealed modest but significant gains made for some memory and attention measures in each of the groups.***

Self practice, presentation of attractive stimuli, multi-sensory feedbacks and personalized training contents were the four different forms of computer-assisted cognitive re-training programmes that **Tam and Man** [76] used to evaluate people with post-head injury amnesia. ***Participants were randomly assigned to one of four treatment groups*** (matched diagnostically and demographically): (1) self-paced group, which allowed individuals to move at their own pace in a non-threatening environment; (2) feedback group, which involved immediate provision of feedback in a non-judgmental fashion; (3) personalized group, whereby the computer presented training contents showing the participant's actual living environment and routines; and (4) the visual presentation group, which was a provision of attractive and bright presentation designed to help individuals engage in the activity. ***Each group went through one of the four computer-assisted memory re-training strategies. Results revealed that the patients in the experimental group showed positive improvements on all of the four memory training methods as compared to the control group.*** However, there were not statistically significant differences among the four training methods. Nonetheless, this study showed that **computer-assisted memory retraining yield positive results for patients with memory post-head injury amnesia.**

Chen et al. [77] studied the ***effect of computer assisted cognitive rehabilitation versus traditional therapy methods.*** Within-group comparisons of pre- and post-intervention measures demonstrated significant gains on multiple psychometric tests taking into account multiple statistical comparisons. However, multivariate analysis comparing the experimental and control groups across the domains of attention, visual-spatial, memory and problem solving ***did not demonstrate significant differences between the groups.***

Gray et al. [78] investigated the ***effects of attentional retraining using a microcomputer-based intervention.*** Patients were stratified into closed-head-injury (CHI) or other diagnosis (17 patients diagnosed as CHI) and mild/moderate or severe injury (15 diagnosed as severe) and randomly assigned to receive either attentional retraining or recreational computing (control). Time since injury varied widely from 7 weeks to 10 years. ***Immediately following training, the treatment group showed marked improvement on two measures of attention in comparison to the control group, however once premorbid intelligence score and time since injury were included as covariates, this treatment effect was no longer significant.*** The experimental group showed continued improvement at 6-month follow-up on tests involving working memory.

Electronic mail (email) may prove useful for reducing the experience of social isolation for patients sustaining acquired cognitive-linguistic impairments.[79] **Sholberg et al.[79]** were interested in the usability and patient preference of a simplified email interface on eight brain injured patients. Patients were asked to read and reply to four prompt conditions: no prompt, idea prompt, fill-in-the-blank prompt and multiple-choice prompt. Difficulties encountered included computer usability and message composition. Results identified three categories of usability problems: lack of knowledge concerning functionality of keys for word-processing operations, poor conceptual understanding for the mouse operation and poor use of interface prompts. Results also found that there was considerable variation among patient preferences and the types of errors observed in composing emails, and that all patients legitimized the use of email interfaces as a means of reducing social isolation.

6.4.3 Amantadine

Q19. What is the evidence for amantadine in improving cognitive functioning post ABI?

Answer

1. There is Level 2 evidence from one RCT that amantadine does not help to improve overall cognitive functioning based on the conclusions of a single RCT.

Discussion

Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist and is currently used as an antiviral agent used as a prophylaxis for influenza A, for the treatment of neurological diseases such as Parkinson's Disease and in the treatment of neuroleptic side-effects such as dystonia, akithesia and neuroleptic malignant syndrome [47]. It is also thought to work pre- and post-synaptically by increasing the amount of dopamine [5].

Schneider et al. (1999) completed a double-blinded, randomized placebo controlled trial evaluating the effects of amantadine on cognition and behavior. Twenty patients were included in the study and each took amantadine for 2 weeks. Statistical comparison of results evaluating the five subsets of attention, executive/flexibility, memory, behavior and orientation ***did not demonstrate any significant effect for the use of amanatadine***.

Study Snapshot

Schneider WN, Drew-Cates J, Wong TM and Dombovy ML. Cognitive and behavioural efficacy of amantadine in acute traumatic brain injury: an initial double-blind placebo-controlled study. *Brain Injury*, 1999:13(11):863-872.

- 10 subjects were selected for inclusion in the following randomly controlled cross over study.
- Subjects were given either amantadine or placebo for 2 weeks, followed by a two week withdrawal period, then amantadine or placebo depending on what they were given first.
- The Neurobehavioural Rating Scale was completed for all participants.
- Cognitive improvement was noted over time, but no significant differences were found between the administration of amantadine or placebo.

6.4.4 Cerebrolysin

Q20. What is the evidence for cerebrolysin in improving cognitive functioning post ABI?

Answer

1. There is Level 4 evidence that cerebrolysin, a neurotrophic and neuroprotective medication appears to have potential benefit to improve outcome and cognitive functioning post-brain injury.

Discussion

As explained by Alvarez et al. [80], "*Cerebrolysin (*EBEWE Pharma, Unterach, Austria*) is a* ***peptide preparation obtained by standardized enzymatic breakdown of purified brain proteins, and comprises 25% low-molecular weight peptides and free amino acids."*** Cerebrolysin has been demonstrated to have neuroprotective and neurotrophic effects, and has been linked to increased cognitive performance in an elderly population.

In an open label trial of 20 brain-injured patients, **Alvarez et al. [80]** investigated the potential benefits of using Cerebrolysin which was administered intravenously 20 times over a 4-week period. Although the study included patients with mild, moderate or severe traumatic brain injury based on the Glasgow Coma Scale score, all patients had significant disability ranging from moderate disability to persistent vegetative state on the Glasgow Outcome Scale. The time since injury varied from 23 to 1107 days with 9 cases less than 1 year post injury and 11 cases greater than 1 year post injury. ***A brief neuropsychological battery (SKT) using 9 tests to specifically evaluate memory and attention demonstrated overall significant improvement for the 9 of 20 patients for whom it could be administered***. Glasgow Outcome Scores also significantly improved comparing pre to post intervention scores.

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