



# *Cognitive Impairments in TBI: Pharmacological Treatment Considerations*

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## **Introduction: Medications Improving Cognitive Functioning**

Traumatic brain injury poses significant and diverse challenges to rehabilitation efforts. Neurobehavioral deficits represent a particularly difficult barrier to rehabilitative progress, return to work efforts and societal reintegration. There are many factors involved in the appropriate and necessary care of each person with cerebral dysfunction. Following acute rehabilitation, individuals with TBI typically are prescribed anticonvulsant medications for six months, and many also may be taking medication for anxiety, depression and/or agitation.

Although these medications may be essential for the individual with TBI, they may not help at all with cognitive functioning and—in some cases—actually may cause and contribute to cognitive dysfunction. Despite dramatic improvements in care of brain injury, there still does not appear to be a commonly used medication or medication regimen that can be used to alleviate or improve cognitive impairments. Though there is substantive research suggesting that some medications may improve cognitive functioning in individuals with cerebral dysfunction, findings are mixed and can be confusing. While many patients and healthcare providers only have anecdotal or misinformation about pharmacological treatment options following TBI, the neuropsychologist may be able to provide useful education and recommendations regarding these issues.

A review of the research literature tends to suggest that individuals may vary dramatically in their ability to benefit cognitively from medication following TBI. Therefore, it is a difficult task to make any gross generalizations regarding the efficacy of certain medications. Additionally, if persons with TBI are in different stages of the spontaneous recovery process, medication effects or perceived medication effects may vary. These individual differences should not serve to preclude individuals from participating trials on potentially helpful medications. Consulting with a neuropsychologist, the physician may be able to monitor the medication effects and changes in cognitive functioning. At the very least, an individual with TBI and his/her family deserve to be educated about potential options.

It is important that neuropsychologists and cognitive rehabilitation therapists know which medications have efficacy in treatment of cognitive dysfunction. This information can assist them and others involved in the care of individuals with TBI to optimize rehabilitation outcomes. Such medications include:

- Many dopaminergic compounds (Karli et al., 1999)
- Sinemet (Lal, Merbtiz & Grip, 1988)
- Aricept (Taverni, Seliger & Lichman 1998)
- Ritalin
- Dexedrine
- Cylert
- Ginko Biloba (Le Bars et al., 1997)
- Vitamin E and Vitamin C (Masaki et al., 2000).

## **Stimulants For TBI and Attention-Deficit Hyperactivity Disorder (ADHD)**

Arguably, the most highly used drug in treatment of cognitive problems is Ritalin (i.e., methylphenidate). It has the highest efficacy of the stimulants for attention deficits (Dopheide, 1999), although it does have a number of side effects and must be prescribed properly. It can be addictive, suppress appetite and can exacerbate nervousness. Stimulants increase frontal lobe activity in individuals who have difficulty regulating that area of brain activity. Frontal lobe dysregulation has been postulated as a pathological process in many individuals with ADHD. Though the frontal lobe dysfunction in ADHD may differ from that frontal lobe dysfunction that occurs post TBI, there may be enough similarity between the conditions to warrant the use of stimulants in TBI.

Ritalin is the drug treatment of choice in ADHD—one of the most common behavioral disorders of childhood (DSM-IV)—and is considered an indirect catecholamine agonist (meaning it indirectly increases or promotes the catecholamine neurotransmitters in the brain). It can enhance cognitive performance including working memory and executive functions in adults and children diagnosed with ADHD (Kempton et al., 1999) and also in normal human volunteers on tasks sensitive to frontal lobe damage, including aspects of spatial working memory performance. The results of a recent study (Mehta et al., 2000) show that the methylphenidate-induced improvements in working memory performance occur with task-related reductions in regional cerebral blood flow (rCBF) in the dorsolateral prefrontal cortex and posterior parietal cortex. Mehta and colleagues indicate that the beneficial effects of methylphenidate on spatial working memory were greatest in the subjects with lower baseline working memory capacity. To our knowledge, this is the first demonstration of a localization of a drug-induced improvement in working memory performance in humans and has relevance for understanding the treatment of ADHD.



The Food and Drug Administration has approved methylphenidate for the treatment of ADHD and narcolepsy. Treatment with methylphenidate also has been advocated in persons with TBI and stroke. Methylphenidate has been researched widely in adult and pediatric/adolescent TBI. After reviewing both controlled and uncontrolled studies, Kraus (1995) concluded that—in general—psycho-stimulants appear to be a reasonable choice for treating certain types of mood, behavior and cognitive symptoms following brain injury. When Whyte and colleagues (1997) treated individuals with TBI with methylphenidate, they found a significant improvement in mental processing speed. Alternatively, there was no improvement in distractibility, sustained attention or measures of motor speed.

Mahalick et al. (1998) evaluated the effects of methylphenidate on a cohort of 14 children with varying degrees of brain injury. As expected, differences between drug and placebo conditions uniformly achieved statistical significance. Their findings suggest that methylphenidate—and probably other psycho-stimulants such as Cylert, Adderal and dextroamphetamine sulfate—is an extremely effective agent in treating attentional disorders secondary to brain injury in children. Psycho-stimulants have been demonstrated to improve deficits of arousal, poor attention, concentration and memory (Karli, Burke & Kim, 1999), and persistent fatigue in those individuals with ADHD. ADHD also may be treated with tricyclic anti-depressants, which have a 50-60% efficacy, only slightly lower than stimulants (Dopheide, 1999).

Perhaps one reason why some of the previously mentioned medications are not more widely utilized is that the research findings are conflicting and, unless thoroughly reviewed, can be misleading. For example, while many studies support the efficacy of stimulants in TBI, Williams et al. (1998) evaluated the use of stimulants in the recovery of pediatric brain injury and did not find stimulants useful. They used the most objective research design (i.e., double-blind, placebo-controlled, crossover design) and administered methylphenidate and placebo. They found no significant differences between methylphenidate and placebo on measures assessing behavior, attention, memory and processing speed.

## **Other Drugs Used to Promote Cerebral Functioning**

Borromei et al. (1997) evaluated the utilization of neuroprotective drugs early post-injury. Eighty-nine participants had undergone traditional therapies and 39 individuals had been given complementary neuroprotective drugs, variously associated with traditional therapies. There was no statistically significant difference between the groups in terms of the global clinical outcome (i.e., assessed by a five-point scale of death, worsening, unchanged condition, improvement and recovery). Statistically, cognitive impairment and depression was significantly less in individuals who underwent conventional therapies and early complementary neuroprotective treatments than in the control group.



There are also some anecdotal cases of persons with TBI having their fatigue successfully treated with anti-Parkinson's medication. Numerous case reports have shown the efficacy of dopaminergics in treating cognitive symptoms (Van Reekum, Bayley & Garner, 1995; Bleiberg, Garmoe & Cederquist, 1993; Kraus & Maki, 1997). Additional medications such as anti-hypertensives like Clonidine have mixed support for the treatment of attentional problems. Early studies have identified dopaminergic drugs such as amantadine, bromocriptine and sinemet as potentially assistive in countering cognitive deficits and fatigue (Karli et al., 1999). Their study demonstrated that through multiple varied dosing schedules, a trade-off between the benefits and side effects of dopaminergic therapy could occur with implications to improve functioning for a larger population of individuals with brain injury.

Apathy occurs frequently in both TBI and neuropsychiatric disorders (i.e., non-Alzheimer's frontal lobe dementia, cerebral infarction, intracranial hemorrhage and alcoholism) and can cause significant functional and rehabilitative difficulties. Agents used to treat this condition included amantadine, amphetamine, bromocriptine, bupropion, methylphenidate and selegiline (Marian et al., 1995).

Although there has been some very successful published case, Amantadine—a medication typically used for respiratory illness—has had mixed results in the research for its utility in improving cognitive functioning following TBI. Van Reekum and colleagues (1995) reported a double-blind placebo-controlled study (N =1) in which an individual with amotivational syndrome following TBI received 100 mg of Amantadine three times a day for four treatment periods of two weeks duration. The individual evidenced significant improvement in symptomatology, with no side effects. Additionally, Edby et al. (1995) published a successful treatment case using this medication. That case involved an 18 year-old boy with anoxic brain injury, exhibiting severe psychomotor inhibition, muscle rigidity and dystonia, that was treated with amantadine in order to ameliorate his symptoms. Neuropsychological tests showed improvement in motor and cognitive functions following treatment.

Sinemet (a mixture of levodopa and carbidopa)—a drug usually prescribed to help persons who have Parkinson's Disease with their motor problems— also has been studied extensively for use in TBI. Lal and colleagues (1988) evaluated the use of Sinemet in 12 individuals with head injury with diffuse brain damage. All of the persons had sustained moderate to severe TBIs resulting in physical, cognitive, communicative, emotional and behavioral deficits. All of the study participants showed functional cognitive and behavioral improvement with Sinemet. Despite possible and probable efficacy of Sinemet, it still is used infrequently in persons with TBI, regardless of how distressing and disabling their cognitive impairments may be.



## Cholinergic Drugs and Brain Functioning

Drugs such as Aricept and Tacrine (i.e., cholinergic agonists) do have proven efficacy in helping slow the progression of memory decline in individuals with Alzheimer's Disease. In fact, these medications specifically were designed to enhance cholinergic functioning in these individuals as they typically have a disproportionate loss of cholinergic neurons in the basal forebrain. Research does appear to support that medication restoring some of the cholinergic functions does enhance cognitive performance.

Although the theoretical basis for cholinomimetic therapy is more indirect with respect to memory disorders complicating acute brain injury, it is accumulating and the specific role of cholinergic systems in experimental and human brain injury has been demonstrated (Hayes et al., 1989). Anecdotal cases and a collection of small studies suggest that Aricept (i.e., donepezil) can help improve memory in TBI and other causes of cerebral dysfunction (Taverni, Seliger & Lichman, 1998). Whitlock (1999) described improvement of five or more points on the Mini Mental Status Examination in persons taking donepezil, who were six months to 16 years post-cerebral injury. While more research is necessary to investigate the effects of Aricept in TBI, it does appear to have some promise in promoting cognitive functioning.

During the past decade, there has been some interest in how estrogen affects cognitive functioning. Several researchers have reported that women who use estrogen replacement therapy perform better on measures of verbal memory, verbal fluency and semantic memory, and have less depression (Phillips & Sherman 1999; Kampen & Sherwin, 1994; Robinson et al., 1994; Henderson et al., 1996; Schneider, Brotherton & Hailes, 1977; Sherwin, 1988).

Robinson and colleagues (1994) compared 72 older women (age range 55-93) taking estrogen replacement therapy with 72 women not on ERT and found that the estrogen replacement therapy group had significantly superior proper name recall, though no significant difference in word recall. Participants were matched on age and education. Kampen and colleagues (1994) also found significantly higher scores in women taking estrogen on measures of immediate delayed recall of paragraphs. No difference was noted on any other cognitive measures. Their conclusion was that estrogen might have a specific effect on verbal memory in healthy post-menopausal women.



## Conclusions

Research has shown that many medications may be helpful in alleviating cerebral dysfunction following brain injury. The medications which do appear to improve cognitive functioning for some individuals are psycho-stimulants such as methylphenidate (i.e., Ritalin), which can improve mental processing speed and attention and perhaps other cognitive abilities. Stimulants do have multiple side effects that may preclude their use in many individuals. Sinemet and amantadine also have appeared to be helpful following TBI, especially in those persons with inertia or an amotivational syndrome. Aricept—which can help memory and cognitive functioning in Alzheimer's Disease and perhaps other types of dementia—may have some efficacy following TBI, although, to date, the data is strictly anecdotal. It also appears that there is an accumulating body of literature supporting Ginko Biloba as something that can produce some mild improvements in cognitive functioning. Though some of the conflicting findings in the research literature may be due to methodological differences, it may be that the significant individual variability of medication effects makes this an especially difficult area for any physician to make gross generalizations.

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