

FOCUS ON PHARMACOLOGY

Tuesday, May 8, 2001





INTRODUCTION TO PHARMACOLOGY IN NEUROREHABILITATION

Henry H. Stonnington, MBBS, M.Sc, FRCP(E), FAAPMR, FAFRM (RACP), Biloxi, MS, USA

The effect of damaging a person's brain function has more long term consequences than any other type of impairment. The individual's subsequent change in behavioral, cognitive, emotional and physical functions, will not only impact that person's future, but will also have significant implications on family structure, fiscal and work responsibilities, and thus have far reaching consequences in the community. As Health Care Givers we need to be guided by the philosophy of holism, and have a team structure, that not only includes professional experts in all these areas, but also the individual in question, the family and appropriate community members. That whole approach is most effective if it is a combination of Prevention, Intervention, Remediation and Amelioration, at every stage of the evolution of the injury. As every aspect of brain function and dysfunction has an impact on its neurophysiology and neurochemistry, the use of pharmacological intervention in general, and neuropsychopharmacological drugs in particular, are an integral part of management.

Acute and preventive interventions: The effect of excitotoxicity in brain damage, such as excessive release of glutamate and subsequent cascade of events of influx of calcium and release of free radicals, activation of nitric oxide synthase, forms a final common pathway that leads to secondary neuronal damage, of neurons and glial cells (1). A great deal of research is being done to try and prevent this secondary damage, which is often worse than the initial injury. This includes the use of pharmacological inhibitors of this pathway, as well as the use of gonadal steroids, and neurosteroids, which specifically modulate astroglia, which have a significant effect on neural function (2).

Coma and minimal consciousness: The use of several dopaminergic drugs such as amantadine and bromocriptine appears to sometime have beneficial results, although the evidence has not been proven (3).

Agitation: It is vital to use the correct neuropharmacological drug very early, such as in the neuro ICU, to keep the use of neurotoxic drugs such as haloperidol at a minimum. Often this needs a cocktail of Valproic Acid, Trazodone (which helps to reverse an aberrant sleep-wake cycle), Buspirone and other similar combinations. Early transfer to the rehabilitation unit with maximum involvement of family and therapists is vital (3, 4).

Long term cognitive, behavioral, depression and community reentry problems: Again the appropriate use of dopaminergic drugs such as amantadine, valproic acid, risperidone in small doses seems to play important (Yet unproven) part. Major depression is an important potential sequella of brain injury, and the use of antidepressants will have to be considered. Is it really wise to use one use the SSRIs, with their depressive effects on sexuality? This and many other applications of



pharmacology has to await many future studies and research. We also need to carefully treat the caregivers, who sometimes suffer as much, if not more, than the effected individual. Pharmacological management has tremendous potential.

References:

- (1) Dugan LL, Choi DW. Excitotoxicity, free radicals, and cell membrane changes. *Ann Neurol*, 35: 17-21;1994
- (2) Garcia-Segura LM, et al, Gonadal steroids and astroglial plasticity. *Cellular and Molecular neurobiology*, 16: 225-237;1996
- (3) Stonnington H.H. *The use of Neuropsychopharmacological agents in the management of persons with brain injury*, In *International perspectives in TBI*, editors Ponsford, Snow, Anderson, Australian Academic Press, 1996
- (4) Cope N. *Psychopharmacological aspects of TBI*. In *Medical Rehabilitation of Traumatic Brain Injury*, Editors Horn LJ, Zasler ND, Henley & Belfus, Mosby: 573-612,1995



TRAUMATIC SAH, VASOSPASM AND CALCIUM ANTAGONIST: AN UPDATE

Franco Servadei, Vincenzo Antonelli, Giuliano Giuliani

WHO Neurotrauma Collaborating Centre, Ospedale M. Bufalini, Cesena, Italy

The clinical importance of traumatic subarachnoid haemorrhage (tSAH) has been first highlighted in 1990 in a report from the USA TCDB¹. Subsequently it was confirmed that from 39% to 45% of patients with severe and moderate head injury has appearance on their CT of tSAH^{1,2,3,4}. The presence of tSAH had an independent effect in worsening outcomes^{1,2,3,4}. The mechanism underlying the link between tSAH and prognosis has not yet been fully clarified. Many works have reported an association between tSAH on CT scan, increased blood flow velocity on TCD studies and decreased CBF. Thus it seems that arterial vasospasm (as for aneurismal subarachnoid hemorrhage) can play a role in the worse outcomes of tSAH patients.

Nimodipine (a calcium antagonist) has been studied in four different trials (nimodipine versus placebo) in head injured patients .

In the HIT I study, 352 head injured patients were studied from 1987 to 1989. The results were slightly in favor of Nimodipine (53% of favorable outcomes versus 49% in the placebo group).

In the HIT II study, 852 patients were included from 1988 to 1991. The overall outcome did not differ, but in the subgroup of tSAH patients, the rate of favorable outcomes were significantly higher in Nimodipine treated patients (51% versus 34%).

HIT III and HIT IV studies were therefore targeted to include only tSAH patients.

HIT III study included only 123 patients (all from Germany) and showed a highly significant difference of favorable outcomes in favor of Nimodipine (73% versus 40%).

HIT IV study included recently 592 patients with mild, moderate and severe head injury. Patients were enrolled in Asia (179), Australia/NZ (61), Europe (159), and South Africa (193).

Overall results did not confirmed previous findings and did not showed any benefit from Nimodipine treatment. It must be noted, anyway, that placebo treated patients with mild-moderate head injury had a rate of favorable outcomes so high (93%) that it is unlikely for any drug to show a benefit. Furthermore, severely head injured patients from Europe (where all previous studies were conducted) had a rate of favorable outcomes of 57% when treated and of 45% in the placebo group.

References:

1. Eisenberg et al, *J Neurosurgery*, 1990
2. Green et al, *J Trauma*, 1996
3. Murray et al, *Acta Neurochir*, 1999
4. Kakariieka A, *Traumatic Subarachnoid Hemorrhage*, Springer, 1997



INTEGRATING PHARMACOLOGY RESEARCH IN LOW-LEVEL COGNITIVE STATES IN CLINICAL PRACTICE

John Whyte, MD, PhD, Moss Rehabilitation Research Institute, Philadelphia, PA, USA

Severe brain injury may result in prolonged periods of unconsciousness (the vegetative state) or questionable consciousness (the minimally conscious state). Approximately half of adults who remain unconscious 1 month after traumatic injury will regain some degree of consciousness by 12 months post-injury. The proportion likely to recover consciousness among those with non-traumatic injuries is lower, and the time interval during which recovery may be expected is shorter.

Initial coma after traumatic injuries is assumed to result primarily from disruption of the function of the reticular activating system (RAS) by diffuse axonal injury. However, the evolution of coma into the vegetative state, with return of sleep/wake cycles and spontaneous respiration, suggests substantial recovery in the RAS. Thus, continued unconsciousness at this point may be due more to disruption of thalamic connections and/or disruption of function in various neural networks that subserve cognition.

The vegetative and minimally conscious states have enormous economic and social costs. Individuals who remain in these states are dependent for all self-care and mobility needs, and often have complex medical needs as well. Many are injured young and with high quality medical care can live for prolonged periods. In addition to their costly medical and custodial needs, such individuals stress the family systems in which they reside. In the United States, some families have no choice but to care for such individuals at home, while other families willingly choose to do so. Each family experiences a unique and complex combination of psychological, physical, and economic burden, mixed with some degree of hope for an improved level of function. Our research on family systems suggests that it may be virtually impossible for families to care for a vegetative family member without maintaining some degree of (often unrealistic) hope for recovery as a source of motivation.

Given the tremendous impact of prolonged unconsciousness on families and society, it is critical to identify ways to improve the prediction of outcome for such individuals, as well as to develop treatments that might improve the current levels of outcome that are possible. The work in our laboratory has focused on 4 inter-related areas:

1. Improving prediction of outcome among individuals with prolonged unconsciousness to assist with treatment planning, family counseling, and planning of randomized clinical trials of promising treatments.
2. Conducting randomized clinical trials of pharmacological and other agents that might hasten recovery of consciousness and/or improve the ultimate level of



outcome reached.

3. Developing methods of assessing profoundly impaired patients' current level of consciousness, and using this information to assess the impact of individualized treatment trials designed to improve the level of consciousness.
4. Studying the beliefs held by families regarding their family member's level of consciousness and comparing these beliefs to objective data regarding cognitive performance in order to develop improved ways of helping families cope with this challenging situation.

This presentation will focus primarily on topic #3 – the evaluation of individual patients' current cognitive function and the use of this information to assess the impact of potential therapeutic interventions.

Assessment of cognitive function in profoundly impaired patients is impeded by their inconsistent behavior, difficulties in differentiating reflexive and spontaneous behavior from inconsistent volitional behavior, and the limitations in clinicians' abilities to form accurate and unbiased impressions of such patients' performance over time. All of these problems demand a quantitative and objective assessment of patient behavior that can be used to define current performance and to track changes in performance associated with treatment interventions.

Our process of initial evaluation of such patients' cognitive function is based on the principles of single subject experimental design. Behaviors that are potentially relevant to the state of consciousness are selected by family and rehabilitation team members during the first 2 - 3 days of evaluation. Frequent questions have to do with whether the patient's state of arousal is sufficient to support conscious processing; whether visual and auditory systems are adequately intact to allow interaction with the environment, and whether certain rudimentary behaviors are evidence of volitional performance. For each such question, the team operationally defines and standardizes the types of stimuli to be administered to the patient (e.g., the verbal commands to be used, visual stimuli to be shown, etc.) and the type of behavior that will be recorded as potential evidence of a response (e.g., a finger movement of a particular magnitude, a lateral eye movement to a visual stimulus, etc.). Appropriate control conditions are also selected (e.g., a specific verbal command vs. a period of silence). Standardized data are collected by all treating therapists throughout the day and are analyzed statistically and graphically to answer the clinical question that was posed.

Once the level of cognitive performance in the absence of pharmacological intervention is defined, these same data elements can form the basis for evaluating response to a drug intervention. Unfortunately, no drug has been unequivocally shown to improve function in vegetative or minimally conscious patients. However, several drugs are promising, based either on theoretical arguments, animal research, or case studies of individual patients. Only randomized clinical trials involving relatively large groups of patients can definitively answer the question of drug efficacy for these



purposes, since this is the only method that powerfully controls for spontaneous recovery and the influence of other concurrent treatments. However, the principles of single subject experimental design can provide some evidence for drug efficacy in individual patients, depending on the drug, the patient's pace of progress, and other factors.

If the baseline evaluation of a patient's cognitive function (e.g., ability to follow verbal commands) is improving rapidly in the absence of specific treatment, it will be very difficult to prove the benefit of an added pharmacological agent. In addition, one might question whether such an agent is clinically appropriate in the context of rapid and positive clinical change. When clinical improvement is slow or absent, however, individualized drug trials may be informative. The most powerful assessment design is a repeated cross-over design (i.e., ABABABABAB.....). Such a design, however, can only be used appropriately when the effects of the drug are anticipated to be fully reversible upon discontinuation; and the drug's actions are rapid and short. Drugs with slower onset of action, but whose effects are still hypothesized to be reversible, can be studied with an ABA design. Drugs which are proposed to induce irreversible positive change can be studied with an AB design. These designs are in decreasing order of scientific rigor, so that, in the latter instances, one can rarely be completely confident that positive changes observed can be attributed to the drug. The high degree of patient variability and the often short time intervals available for evaluation also compromise the ability to obtain definitive results. Although statistically significant results may not be obtained in many of these drug evaluations, gathering and analyzing objective performance data can still improve clinical decision making beyond that possible through clinical observation alone.

References:

- Whyte J: *Clinical drug evaluation. J Head Trauma Rehabil* 3(4):95-99, 1988
- Whyte J: *Toward rational psychopharmacological treatment: integrating research and clinical practice. J Head Trauma Rehabil* 9(3):91-103, 1994
- Whyte J, DiPasquale M: *Assessment of vision and visual attention in minimally responsive brain injured patients. Arch Phys Med Rehabil* 76(9):804-810, 1995
- Reinhard DL, Whyte J, Sandel ME: *Improved arousal and initiation following tricyclic antidepressant use in severe brain injury. Arch Phys Med Rehabil* 77(1):80-83, 1996
- DiPasquale M, Whyte J: *The use of quantitative data in treatment planning for minimally responsive patients. J Head Trauma Rehabil* 11(6):9-17, 1996
- Phipps E, DiPasquale M, Blitz C, Whyte J: *Interpreting responsiveness in persons with severe traumatic brain injury: beliefs in families and quantitative evaluations. J Head Trauma Rehabil* 12(4):52-67, 1997
- Laborde A, Whyte J: *Update on Pharmacology. Two dimensional, quantitative data analysis: its role in assessing the functional utility of psychostimulants in minimally conscious patients. J Head Trauma Rehabil* 12(4):90-92, 1997
- Phipps E, Whyte J: *Medical decision-making with persons who are minimally*



- conscious. Am J Phys Med Rehabil 78(1):77-82, 1999*
- Whyte J, DiPasquale M., Vaccaro M: *Assessment of command-following in minimally conscious brain injured patients. Arch Phys Med Rehabil 80:1-8, 1999*
 - Whyte J, DiPasquale M, Childs N, Keating D, Katz D, Kalmar K, Novak P, Mercer W, Long D, Journey-Merges B, Moheban C, Giacino J, Van Wie S: *Recovery from the vegetative and minimally conscious states: Preparation for a multicenter clinical trial. (Abstract) Am J Phys Med Rehabil 78(2):181, 1999*
 - Whyte J, Laborde A, DiPasquale MC: *Assessment and treatment of the vegetative and minimally conscious patient. In Rosenthal M, Griffith ER, Kreutzer JS, Pentland B (eds.), Rehabilitation of the Adult and Child With Traumatic Brain Injury (3rd Ed.), Philadelphia: F.A. Davis, 25:435-452, 1999*



MOOD AND BEHAVIOURAL DISORDERS AFTER TBI: A PSYCHOPHARMACOLOGICAL APPROACH

Riccardo Torta, Department of Neuroscience, University of Torino, Italy

Several psychiatric sequelae can follow traumatic brain injuries (TBI). Depressive, behavioural, psychotic and anxiety disorders are related to a multifactorial pathogenesis in which brain damage, premorbid personality and social-environmental context are strictly related.

A strict psychiatric categorial diagnostic approach is poorly useful and clinicians should pay more attention to the dimensional psychopathological context, in which target symptoms would be identified.

Moreover, psychopharmacological choice must be based not only on symptomatological clusters criteria, but also on effectiveness and safety of each drug in order to the peculiar clinical situation of each patient with TBI.

Primary attention will be paid to the post-traumatic epileptogenic risk, with exclusion of those drugs that demonstrate a greater proconvulsant activity, such as tricyclic antidepressant (at high dosages), maprotiline, amoxapine, clozapine. Another problem is represented by the neurocognitive toxicity: in order to avoid it, anticholinergic and antihistaminergic drugs should not be used. Also psychotropic drugs that can interfere with the rehabilitative process, through a sedative or fatigant side effect, must be avoided.

Frequently clinical psychopathological pictures in patients with TBI must be referred more to a syndromic spectrum than to a single symptomatological dimension: so concomitant management of depressive, manic and behavioral features is needed. In this context psychotropic drugs with a broad spectrum of action (such as SSRIs, SNRIs and Atypical Antipsychotics) can represent a first choice treatment, simultaneously acting on depression, aggressiveness, anxiety, cognition and emotional lability. Several drugs of these classes also demonstrate less extent of side effect concerning cognitive, convulsive and organic problems in TBI patients. compared to the first generation of psychotropic drugs (such as TCA, Neuroleptics and Benzodiazepines).



NEW ANTIEPILEPTIC MEDICATIONS

Francesco Monaco, Neurological Clinic, University "Amedeo Avogadro", Novara, Italy

The history of antiepileptic drug (AED) therapy goes back to the beginning of the last century, when phenobarbital (PB) was first employed as an anticonvulsant (1912). After that, diphenylhydantoin (PHT), ethosuximide (ESM), primidone (PRM) and a few other minor agents were discovered in the following years up to the 50's. In the early 60's, carbamazepine (CBZ) and valproic acid (VPA) appeared as new and very promising drugs, and as more experience was gained from a great number of clinical and experimental studies, they were confirmed as being two major AEDs. About twenty years later the explosion of renewed research in the area took place, and the new drugs oxcarbazepine (OXC), vigabatrin (GVG) and lamotrigine (LTG) were introduced into antiepileptic therapy (80's). soon followed by felbamate (FLB), gabapentin (GBP) tiagabine (TGB), topiramate (TPM) and, in some countries, levetiracetam (LEV) and zonisamide (ZNS).

The mechanism of action of these new AEDs is not fully understood: however, the common link among them is their ability to modulate excitatory and inhibitory neurotransmission by affecting a number of sites such as ion channels, neurotransmitter receptors and neurotransmitter metabolism. In particular, 1) OXC blocks the voltage dependant sodium channels; 2) GVG increases brain GABA concentration by irreversibly blocking GABA transaminase; 3) LTG blocks sodium currents, increases brain GABA concentrations, decreases glutamate release, provides neuroprotective effect secondary to inhibition of glutamate release; 4) FLB blocks NMDA-induced current at the glycine or NMDA site, enhances GABA-evoked chloride currents, limits sodium action potential firing; 5) GBP increases GABA synthesis, limits high-frequency action potential firing, reduces L-calcium currents, increases free plasma serotonin, protects against glutamate neurotoxicity; 6) TPM blocks sodium currents, blocks the AMPA glutamate receptor subtype, increases brain GABA concentrations, enhances GABA-evoked chloride currents, inhibits carbonic anhydrase isoforms, possibly inhibits L-calcium currents; 7) TGB inhibits GABA reuptake by blocking its selective transporter; 8) ZNS blocks sodium and T-calcium channels, increases brain DA content. The precise mechanism by which LEV exerts its antiepileptic effect is unknown, and does not appear to derive from any known mechanism involving inhibitory and excitatory neurotransmission.

Compared with older agents, many of the new drugs exhibit simpler pharmacokinetics. This is especially true for GVG, LEV and TGB, which are renally eliminated and have a low interaction potential. Unlike most of the older agents, GVG, GBP and TGB are devoid of significant enzyme inducing or inhibiting properties. TPM, OXC and FLB may induce the metabolism of steroid oral contraceptives. In addition, FLB acts as a metabolic inhibitor. To date, the efficacy of the new AEDs has been evaluated



extensively only under add-on conditions in patients with partial seizures, with or without secondary generalization, refractory to conventional treatment. However, there is evidence that LTG, FLB and possibly TPM may also be effective in generalized epilepsies. In placebo-controlled studies, typically between 15 and 40% of patients with severe epilepsy have shown an improvement, defined as a 50% or greater decrease in seizure frequency, with only a small minority of patients becoming seizure-free.

Compared with older agents, some of the new drugs may have a better tolerability profile. However, FLB has been associated with a high risk of aplastic anemia and hepatotoxicity, and GVG causes peripheral visual field defects in a high percentage of patients. To a lesser extent, TPM may cause weight loss and nephrolithiasis; GBP ataxia, tremor and behaviour disturbances; LTG and OXC skin rashes, LEV infection (flu syndrome).

Further studies are needed to characterize the activity spectrum of these new AEDs and the relationship between their cost and efficacy.

References:

- Feely M. *Drug treatment of epilepsy. BMJ 318: 106-109, 1999*
- Moshe L.S. *Mechanism of action of anticonvulsant agents. Neurology 56 (Suppl 1): S32-S40, 2000*
- Perucca E. *The new generations of antiepileptic drugs: advantages and disadvantages. Br. J. Clin. Pharmacol. 42: 531-543, 1996*



TREATMENT OF SLEEP DISTURBANCES AFTER TBI

Antonio Vela-Bueno, MD, Professor at the Department of Psychiatry, Universidad Autónoma, Madrid and clinical professor, Department of Psychiatry, Pennsylvania State University, USA

Sleep disorders are commonly found among patients suffering traumatic brain injuries (TBI) of various degrees of severity. They can be part of both the acute and chronic behavioral manifestations of TBI. Thus, they can be a symptom of an anxiety disorder, a mood disorder or a psychotic disorder. On the other hand, sleep disturbances can be the chief complaint. Etiological factors contributing to the appearance of sleep disorders in TBI belong to different categories, including the lesion itself, psychopathology and drugs used to treat the general condition.

The occurrence of sleep disorders in patients who sustained a TBI has implications in the clinical course and prognosis of the general condition. Actually they may interfere with the cognitive, affective and behavioral outcome of the TBI. Therefore their early diagnosis and proper management are of paramount importance.

There is relative lack of consistent information on sleep disorders occurring in TBI patients; the existing studies suggest that they are underreported. Consequently there is a lack of available evidence regarding specific treatment strategies, including the pharmacological area, with the exception of a limited number of anecdotal reports. Thus, there are not well controlled studies on the pharmacology of sleep disorders in TBI patients. Therefore there are not well established benefit to risk ratios in the use of commonly use drugs in these patients.

The two most commonly found dysomnias in TBI patients are insomnia and excessive daytime sleepiness in its various clinical presentations. Less frequently described are the disorders of the circadian sleep wakefulness rhythm, although clinical experience suggest they may be more prevalent than it is thought. There are only a few reports on parasomnias in TBI patients.

The pharmacological treatment of sleep disorders in TBI patients, like with other clinical populations, should be part of a comprehensive multidimensional approach including pharmacological and nonpharmacological approaches. They include, in addition to drug treatment, sleep hygiene, psychotherapy and cognitive-behavioral therapy. The treatment plan should be tailored to the needs of each individual patient and to his/her cognitive, affective and behavioral status.

Pharmacological treatment

Three main types of drugs are used, generally speaking, in the treatment of sleep



disorders: hypnotics, stimulants and chronobiotics. Other drugs that may be necessary are those used in the treatment of nosological entities of which sleep disorders can be one the symptoms. Thus, some patients may need to be treated with anxiolytics, antidepressants (these are used also for some primary dysomnias such as narcolepsy), anticonvulsants and neuroleptics, alone or in different combinations. In this presentation we will focus on hypnotics, stimulants and chronobiotics.

The use of hypnotics in the treatment of insomnia in TBI patients should follow the same guidelines used for other clinical populations: a) rule out sleep apnea and COPD; b) assess the organic brain condition; c) use them as adjunctive treatment; d) use the lowest effective dose; e) assess the development of tolerance; f) identify expected adverse reactions such as daytime sedation; g) identify unexpected adverse reactions, such as daytime anxiety and delayed amnesia h) identify withdrawal reactions, such as rebound insomnia. The above guidelines are crucial to establish the risk to benefit ratio of each drug in any individual patient. The knowledge of the pharmacokinetics and pharmacodynamics of each drug is fundamental to make the right choice with each patient. In general, the use of hypnotics in TBI patients has to take into consideration their increased vulnerability to adverse reactions.

Stimulants are used as the main class of drugs in the treatment of some excessive daytime sleepiness disorders such as narcolepsy and different hypersomnias. Their use should follow some rules, taking into consideration, among other features, their potential to produce tolerance and dependence as well as their peripheral effects.

Chronobiotics, drugs that reset the circadian clock, have their main indications in the treatment of the disorders of the circadian sleep-wakefulness rhythm. There are isolated reports showing the efficacy of melatonin, the main representative of this class of drugs, in the treatment of a circadian disorder following a TBI.

Other types of drugs that have been used with success in TBI patients with various sleep disorders have been antidepressants and lithium among other. As with the other types of drugs there are only anecdotal reports.

In summary, well conducted controlled studies are lacking in the pharmacological treatment of patients presenting with sleep disorders following TBI. Considering the elevated prevalence of these conditions this is an area that deserves much more attention.



THE PROBLEM OF COGNITIVE ENHANCEMENT: DO NEUROTROPICS WORK?

Zeev Groswasser, MD, M.P.H., Loewenstein Rehabilitation Hospital, Ra'anana, Sackler Faculty of Medicine, Tel-Aviv University, Israel

Objectives:

1. To present the current clinical use of various drugs which probably enhance cognitive recovery following TBI.

Decreased capacity to process information is one of the main sequelae of traumatic brain injury (TBI). Improving cognitive capacity following severe TBI has therefore become one of the key fields of TBI rehabilitation. It is quite established that traditional ways of treatment are helpful but long periods of treatment are needed. The better understanding of cellular mechanisms underlying human performance has prompted research into the possible role of neurotrophics in improving cognitive performance following TBI.

Diffuse axonal injury (DAI) is the underlying pathology in TBI. DAI may affect superficial and deep brain structure, and disrupt various neurotransmitters systems (biogenic amines, amino acids, peptides and gases). Disruption in their well coordinated and balanced simultaneous action occurs following brain damage, affecting brain basic functions like cognition and behaviour. A large body of non-human experimental data has been accumulated, building pressure on clinicians working in the field of TBI rehabilitation to use nootropics to enhance cognitive recovery. Economic pressure on rehabilitation systems has markedly increased in recent years. The need to produce results under economic restraints has further motivated practitioners to look for new pharmacological agents in order to provide better therapy at shorter time periods. Search for possible help from medications used in deterring neurodegenerative diseases like Alzheimer's Disease, were also considered in TBI patients. It is quite complicated, if not impossible altogether, to separate metacognitive functions from cognitive and behavioural aspects of human performance. Not surprisingly, very few well documented double blind controlled studies exist in TBI literature. Open trials and clinical impressions must therefore serve as reliable sources until further data is available. One must look at data available in other pathological conditions like Alzheimer's Disease and the effect(s) of anxiety on cognitive performance, especially attention and memory. However, only few drugs like Amantadine, Methylphenidate (Ritalin), Bromocriptine and Donepezil have been used in TBI practice and will be discussed. The role of antidepressive and anxiolytic drugs will be discussed as well. It is our clinical impression that the combination of amantadine and methylphenidate is more effective than either drug given alone. It may well be that "classical" trials using one drug at the time will fail to provide sound data and only timely given balanced combinations of drugs will provide the much expected improvement of cognitive function in TBI patients.



