

Review of Awakening Agents

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ABSTRACT: Brain injuries are a serious burden of illness to Canada and the US. Advances in managing head trauma have allowed more patients to emerge from decreased levels of consciousness and helped them cope with neurocognitive, neurobehavioural, and neuropsychiatric deficits. In this article, we review the current (1986-2002) evidence surrounding the pharmacological management of arousal states and the aforementioned neurological sequelae of head injury in either acute or chronic conditions. This article will review the evidence for the use of psychostimulants (methylphenidate), antidepressants (amitriptyline, selective serotonin reuptake inhibitors, and bupropion), Parkinson's medications (amantadine, bromocriptine, carbidopa/levodopa), anticonvulsants (valproic acid), modafinil (Provigil), lactate, hyperbaric oxygen chamber, electroconvulsive therapy, and transcranial magnetic stimulation, in patients following a head injury. The review did not include all anticonvulsants, neuroleptics, beta-blockers, benzodiazepines, azospirones or cognitive enhancers. Unfortunately, the quality of the evidence is generally poor, and sometimes conflicting, which in turn results in indecisive guidelines for treating patients. Accepting the inherent flaws in the evidence we feel that this paper may serve as a stepping-stone for future researchers to improve data gathering that targets neurocognitive, neurobehavioural and neuropsychiatric symptoms following a head injury.

RÉSUMÉ: Revue sur les agents d'éveil. Les traumatismes cérébraux constituent un lourd fardeau au Canada et aux États-Unis. Les progrès dans la prise en charge des traumatismes crâniens ont permis à plus de patients d'émerger d'un niveau de conscience altéré et les ont aidés à s'adapter à des déficits neurocognitifs, neurocomportementaux et neuropsychiatriques. Dans cet article nous revoyons les données publiées depuis 1986 sur le traitement pharmacologique d'un état de conscience altéré et des séquelles neurologiques des traumatismes crâniens mentionnés précédemment, en phase aiguë ou chronique. Cet article revoit les données appuyant l'utilisation de psychostimulants (méthylphénidate), d'antidépresseurs (amitriptyline, inhibiteurs sélectifs de la recaptation de la sérotonine et bupropion), d'anti-parkinsoniens (amantadine, bromocriptine, carbidopa/lévodopa), d'anticonvulsifs (acide valproïque) de modafinil (Provigil), de lactate, d'oxygénothérapie hyperbare, d'électrochocs et de stimulation magnétique trans-crânienne chez des traumatisés crâniens. Nous n'avons pas inclus l'utilisation de tous les anticonvulsifs, de tous les neuroleptiques, bêtabloquants, benzodiazépines, azospirones ou facilitateurs cognitifs. Malheureusement, la qualité des données est généralement médiocre et parfois elles sont contradictoires, ce qui donne lieu à des lignes directrices ambiguës quant au traitement de ces patients. Le fait de reconnaître les lacunes de ces données peut servir de prémices à une amélioration dans la collecte des données sur les symptômes neurocognitifs, neurocomportementaux et neuropsychiatriques chez les traumatisés crâniens.

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Head injuries represent a significant burden of illness. In the United States, where the incidence is approximately 200 per 100,000 population, head trauma accounts for 12% of all hospital admissions, and is associated with a mortality rate of 25 per 100,000.¹ However, with advances in the management of head traumas, there are more individuals who are either in, or emerging from, a state of decreased level of consciousness (LOC).² Moreover, there is a growing body of evidence that suggests that medical or pharmacological interventions can alleviate two important consequences of brain injury: postinjury neurological impairments and decreased LOC.

Neurological symptoms related to the dysfunction of higher

cortical functions can be divided into three categories: neurocognitive (NC), neurobehavioural (NBH) and neuropsychiatric (NP). Neurocognitive deficits involve amnesic disorder, attention deficits, decreased mental processing, poor

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executive functioning, poor insight, disorientation, motor retardation, and perseveration.³ Neurobehavioural deficits include irritability, hyper-excitability, nervousness, disinhibition, poor impulse control, restlessness and aggression, with aggression and agitation seen in as many as 30% of brain injuries.^{4,5} Lastly, NP deficits commonly involve mood disorders such as depression and mania, as well as personality changes that are primarily characterized by disinhibition and egocentricity.³

Traumatic brain injury (TBI) is graded as mild, moderate, or severe based on the LOC or the Glasgow Coma Scale (GCS) score after resuscitation. A GCS score between 13 and 15 characterizes mild TBI. In most cases it represents a concussion, and there is full neurological recovery, although many patients reveal short-term memory and concentration difficulties. Patients with moderate TBI are typically stuporous and lethargic with a GCS score between 9 and 13. A comatose patient unable to open his or her eyes or follow commands, with a GCS score of less than 9, by definition has a severe TBI.

Patients with head injuries present with varied LOC: coma, vegetative state (persistent), akinetic mutism, locked in state, and minimal consciousness (ranging from most to least severe, respectively). Coma is defined as the absence of arousal, sleep wake cycles, and spontaneous eye opening.^{6,7} In a vegetative state, a patient shows no signs of cortical functioning, but does have brainstem activity that allows for respiratory function. Unlike coma patients, these patients may have sleep-wake cycles, show signs of tracking, and at times show spontaneous movement of limbs.⁸ Akinetic mutism is a behavioural state, in which a patient appears awake but does not move or speak,⁹ it can be detected with returned sleep cycles even though there is no external evidence of any mental activity.¹⁰ The locked in state is characterized by spastic quadriplegia, absent cranial nerve function except for sparing of vertical eye movements, blink, and occasionally horizontal eye movements. Level of consciousness is usually intact.¹⁰ If any other voluntary motion is identified, the condition is not a locked in state.¹⁰ The minimal consciousness state is a condition of severely altered consciousness in which minimal but definite behavioural evidence of self or environmental awareness is demonstrated.² These patients begin to demonstrate and re-establish voluntary behaviours that signal internal states and concerns.¹¹

Traumatic head injury may result in either diffuse or localized brain injury. Most traumatic brain injuries result in widespread damage to the brain exerted by shearing forces during rapid accelerations and decelerations during impact. This mechanism may produce both focal and diffuse axonal injury, as well as localized damage at the sites of brain's impact against the skull. The brainstem, frontal lobe, and temporal lobes are particularly vulnerable to this because of their close proximity to bony protrusions.

Imaging and clinical findings are both of use in determining the location of the injured regions. The frontal lobe is almost always injured due to its large size and its location near the front of the cranium. Clinical findings consistent with frontal lobe injury (non orbito-frontal) include simple motor seizures, contralateral hemiplegia, and Broca's aphasia as well as psychiatric symptoms of disinhibition, apathy, mania and emotional lability.^{11,12} Parietal lobe lesions are suggested clinically by the presence of sensory seizures, contralateral hemisensory loss, and

inferior visual field loss, anomia, alexia, agraphia, dyscalculia, constructional apraxia, delusions, auditory/visual hallucinations and minor depression.^{11,12} Patients with occipital lobe lesions will display simple partial seizures, a contralateral homonymous hemianopia, visual field cuts, color and movement agnosia, alexia without agraphia and visual hallucinations.^{11,12} Temporal lesions are characterized by absence seizures, olfactory and complex visual and auditory hallucinations, contralateral superior visual field loss, prosopagnosia, categorization, as well as Wernicke's aphasia.^{11,12} Delusions, anxiety and mania may also be present. Unilateral brainstem lesions cause ipsilateral cranial nerve dysfunction, contralateral spastic hemiparesis, hyperreflexia, extensor plantar response, contralateral hemisensory loss, ipsilateral diminished coordination, dysphasia and vertigo.^{11,12} Bilateral brainstem lesions destroy respiratory and circulatory centres leading to coma and death.¹¹ Finally, cerebellar lesions are indicated by loss of postural control, unsteady gait, intention tremor, dysarthria, cerebellar ataxia, vertigo and nystagmus.^{11,12}

Even in light of the clinical manifestations noted above however, lesion localization remains a difficult process. The addition of diagnostic imaging can be useful in many head traumas, but CT scans (the imaging modality of choice in the acute setting) reflect only destruction, not dysfunction. It is also worth noting that lesion localization has shown poor correlation to treatment response.¹¹

Neuropharmacological agents are routinely used in brain-injured patients and these agents appear to play a multifaceted role in the treatment of moderate to severe head injuries.^{13,14} Their main role is to restore the balance of neurotransmitters, as there is a noted alteration within the spinal fluid of individuals after injury.¹⁴ What many of these studies do not address, however, is that in addition to neurotransmitter depletion, hormone regulation is disrupted in brain injuries involving shearing forces, which disrupt the hypothalamic-pituitary axis.

The 'Lund' concept also emphasizes the complications of a head injury.¹⁵ One of the Lund concepts addresses the importance of microcirculation surrounding brain contusions in order to avoid cellular hypoxia and death.¹⁵ One study has shown the benefits of prostacyclin in optimizing this circulation.¹⁵ Most of the agents, which are included in this review, only examine elevation of neurotransmitters and thereby exhibit limited application to other hypotheses. A list of common pharmacological agents for the purposes of managing brain injury was generated from the literature and clinical experience.

Psychostimulants, such as methylphenidate, which blocks reuptake of dopamine via binding to dopamine transporters, thus increasing extracellular dopamine levels, has been used as an analeptic for reversal of barbiturate-induced coma.¹⁶

Antidepressants are also used to manage brain injury. Amitriptyline, one of the tricyclic antidepressants, prevents reuptake of serotonin and norepinephrine.¹⁷ The rationale for its use is that serotonergic and adrenergic fibres are located near the frontal lobes, and the frontal lobe is the most common site of traumatic contusion.¹⁷ As a result, serotonergic and adrenergic fibers are at risk during TBI. Increasing serotonin may be useful because some studies suggest that serotonin plays a major role in stabilizing and coordinating brain function.¹⁸ As a class, selective serotonin reuptake inhibitors (SSRI) medications have

been reported to be useful in treating behavioural syndromes in TBI patients, especially among patients who are in the early stages of recovery.¹⁸ Similarly, in addition to increasing dopamine levels, bupropion has also been used to increase serotonin levels.¹⁹

Medications used to treat Parkinson's syndrome also help with brain injury, such as amantadine (Symmetrel),²⁰ bromocriptine and carbidopa/levodopa. Amantadine acts pre-synaptically to enhance dopamine release or inhibit its reuptake, and can act postsynaptically to increase the number of receptors, or to alter the receptor's configuration.²⁰ It is commonly used in the treatment of Parkinson's, but also treats side effects due to neuroleptic use, such as dystonia, akathisia and neuroleptic malignant syndrome.²⁰ Bromocriptine is a dopamine receptor agonist affecting primarily D2 and partially D1 receptors.²¹ D2 sites play a major role in the head injured patients in controlling NP and NBH problems.²¹ D2 sites also affect the nigrostriatal region, an important site in the pathology of Parkinson's and schizophrenia.²¹ These receptors are also found in areas of the brain affecting speech. Carbidopa/levodopa (Sinemet) have also been effective, as they directly increase levels of dopamine. Levodopa becomes dopamine once decarboxylated, while carbidopa inhibits the decarboxylase allowing time for levodopa to reach the CNS.²¹

Anticonvulsants have also been used to treat symptoms of TBI. As an example, valproic acid enhances GABA-ergic mediated inhibitory control, thus promoting general CNS stabilization.²² Besides its anticonvulsant effects, valproic acid has also been used in mania, schizoaffective disorder, bipolar disorder, post-traumatic stress disorder, panic states, and behavioural syndromes.²²

A variety of other agents have also been found to be useful amongst head injured patients. These include modafinil, (Provigil),²³ lactate, hyperbaric oxygen chamber,²⁴ electroconvulsive therapy (ECT),²⁵ and transcranial magnetic stimulation (TMS). Modafinil is a vigilance promoting medication that is commonly used to treat narcolepsy (which can present with similar symptoms found in TBI such as excessive daytime sleepiness, inattention and decreased ability to perform social activities). Modafinil's activity is specific to the anterior hypothalamus, hippocampus and amygdala.²⁶ At these sites it is thought that modafinil has some inhibitory effect on GABA, or may be involved in increased levels of glutamate.²⁷ Lactate is also used to treat brain injury as recent studies have shown neurons to carry out synaptic function with lactate as the only available carbon source.²⁸ In terms of TBI, levels of lactate can also correlate with the severity of injury, the time after injury and the level of glucose available for metabolism.^{29,30} Hyperbaric oxygen therapy is used because brain injury may result in inadequate oxygen to the brain, and can result in the conversion of aerobic glucose metabolism to anaerobic metabolism. This anaerobic metabolism results in acidosis and depletion of cellular energy.²⁴ Hyperbaric oxygen therapy may be useful because it can improve the oxygenation of ischemic tissues and lower intracranial pressure. Lastly, ECT has been used for treating brain injury as well. Although ECT has been used to alleviate symptoms of mental illness for the past 50 years, not much has been learned about how ECT works to relieve severe depression.²⁵ Transcranial magnetic stimulation has been used for

similar reasons, and works by passing current through a hand-held coil to generate a magnetic field. This magnetic field is then passed through the skull and into the brain. These well-controlled, small-induced currents can stimulate specific areas of the brain.³¹

METHODS

The purpose of our review was to examine the literature in the treatment of depressed LOC, NC, NBH and NP disorders amongst head injured patients in both the acute and chronic setting. The literature search involved using the database Medline, with the earliest article dating back to 1986. The keywords used to perform the search were "traumatic brain injury", which was then subsequently combined with the search words "methylphenidate", "antidepressants", "amantadine", "bromocriptine", "anticonvulsants", "electroconvulsive therapy", "transcranial magnetic stimulation", and "hyperbaric oxygen therapy". Each article was reviewed looking at a number of subjects, acute versus chronic treatment (with acute being less than one month), the condition that was treated (as implied by the authors whether it presented NC, NBH or NP symptoms), arousal state that was treated (coma, vegetative state, akinetic mutism, locked in state, minimally conscious), average dose of medication, study design and lesion type (traumatic vs. nontraumatic). All data was reported as unavailable if we were unable to obtain this from the article. The review was limited mostly to human and English studies, with one study conducted in rats. The quality of evidence in the reviewed studies was graded using a new system for recommendations in evidence-based medicine compiled by Harbour and Miller.³² Grade A recommendations are based on evidence from meta-analysis, systematic reviews, or randomized controlled trials directly applicable to the target population or on systematic review of randomized controlled trials or a body of evidence consisting principally of studies applicable to the target population and demonstrating overall consistency of results. Grade B recommendations result from high quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal. Grade C recommendations come from well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal. Finally Grade D recommendations come from nonanalytic studies such as case reports, case series and expert opinions. The aforementioned gradation of study quality corresponds to varying levels of evidence as determined previously by the Canadian Network for Mood and Anxiety Treatments.³³ Specifically, Grade A recommendations are used to establish Level I evidence, Grade B and C recommendations produce Level II evidence, and Grade D evidence produces Level III evidence.³³

RESULTS

Methylphenidate

A number of studies looked at the role of methylphenidate in the treatment of patients with brain injuries (Table 1). Methylphenidate appears to be useful in either acute or chronic setting, where the location of the lesion does not play a vital role

Table 1: Methylphenidate and its role in brain injuries

Methylphenidate Dose	Lesion	Time (acute <1 month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
0.3 mg/kg bid ⁴¹	Not Assessed (N/A)	Acute	Neurocognitive: • attention, speed of mental processing and memory were improved • enhances rate, but not level of recovery	Double blind placebo controlled with random assignment N=23, Grade B
10 mg bid ³⁸	N/A Right cerebral herniation into left cranium	Acute Acute	N/A	Case study N=2, Grade D
15 mg bid ³⁹	Diffuse	Acute	Neurocognitive: • speed of mental processing and memory improved • attention improved in short term only	AABA design (pt was own baseline) N=11, Grade D
0.25 mg/kg bid ⁴⁰	N/A	Acute- chronic	Neurocognitive: • mental processing speed improved • no change in attention	Randomized placebo control N=19, Grade B
30 mg ³⁵	Diffuse	Chronic	Neurocognitive: • memory improved • no increase in attention Neurobehavioural: • decreased agitation	Randomized, pre-test, post test N=38, Grade B
Unknown ³⁶	N/A	Chronic	• Reduced seizures	Longitudinal study N=30, Grade C
0.3 mg/kg bid ³⁷	N/A	Chronic	• No benefits in attention, learning, cognitive speed	Double blind control study N=12, Grade B
0.3 mg/kg bid and dextroamphetamine, 0.2 mg/kg/bid ⁴²	Diffuse	Chronic	Neurobehavioural: • decreased agitation Neurocognitive: • improved speech memory and attention	Case studies, Grade D
5 mg and dextroamphetamine = 2.5 mg ³⁴	N/A	Chronic	Neurocognitive: • disorganization, attention, memory impulsiveness, and lability improved	Literature review of 11 studies, Grade A

bid = twice a day; pt = patient; AABA= prospective multiple baseline design (A=baseline period, B=intervention period)

in the management. The main indications for its use in brain injury patients include improving NC and NBH deficits, specifically attention, speech, memory, cognitive processing, and agitation.

In one study, patients were treated with 5 mg of methylphenidate and 2.5 mg of dextroamphetamine.³⁴ An improvement was observed in such NC functions as ability to organize, attention, memory, impulse control and lability (Grade A).

Two separate studies, which looked at NBH problems, showed that methylphenidate was effective in the treatment of agitation and seizures (Grade B + C).^{35,36} Conflicting data has also been shown; however, in one study in which methylphenidate showed no NBH benefit (Grade B).³⁷

In a majority of studies methylphenidate was administered twice a day, either at a fixed dose of 10-15 mg³⁸⁻⁴⁰ or at a dose of 0.3 mg/kg.^{37,40,41} All but one of these studies showed that the use of methylphenidate at these doses resulted in improvement in

such NC functions as attention, speed of mental processing and memory (Grade D). Treatment with 0.3 mg/kg dose of methylphenidate and 0.2 mg/kg of dextroamphetamine twice a day resulted in NBH benefits as well as an improvement in speech, memory and attention (Grade D).⁴²

Amitriptyline

Table 2 summarizes the role of amitriptyline in the treatment of brain injury. Amitriptyline may be mildly effective in treating brain injury patients in the chronic setting, in situations where the lesion is not isolated to one specific area. A majority of the evidence for amitriptyline use has come from case reports.

Two studies used a dose of 150 mg in the treatment of either acute or chronic agitation following a brain injury.^{14,17} The quality of these two studies differed (Grade D and B, respectively).

A separate study examined the effect of combining 50 mg of

Table 2: Amitriptyline and its role in brain injury

Amitriptyline Dose	Lesion	Time (acute <1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
150 mg ¹⁷	N/A	Acute	Neurobehavioural: • decreased acute and chronic agitation	Randomized N=35, Grade B
Amitriptyline, 50 mg Desipramine 50-75 mg ⁴³	Bifrontal left parietal Diffuse axonal injury	Chronic	Neurocognitive: • improved verbalization and arousal	3 case studies, 2 of which had ABAB, Grade D
150 mg ⁴	Diffuse	Chronic (2yrs)	Neurobehavioural: • decreased acute and chronic agitation	Case-study, Grade D

ABAB = fixed allocation randomization (initial A=baseline measurement period, initial B=treatment measurement period, second A=withdrawal of treatment measurement period, second B=reintroduction of treatment measurement period.

Table 3: SSRIs and their role in brain injury

SSRI Dose	Lesion	Time (acute<1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
Sertraline 100 mg/day for 2 weeks ¹⁹	Diffuse, MVA	Acute	Tested for agitation, recent memory, orientation (alertness) • no benefit	Case control series, randomized placebo-controlled, cross over design N=11, Grade C
Citalopram 20 mg/ day with carbamazepine (600 mg a day) ⁴⁶	N/A	Acute – Chronic	1) Neuropsychiatric: • Beneficial effects in major depression 2) Neurocognitive: • decreased anxiety 3) Neurocognitive: • disorganization and psychomotor slowness improved	No placebo group, comparison group was acute or chronic TBI, Grade D N=20
Sertraline: 25-200 mg/day for 8 wks. ⁴⁴	Mild traumatic brain injury	Chronic	1) Neurobehavioural: • improved agitation 2) Neurocognitive: • improved psychomotor speed, recent memory, and depression	Non-randomized, single, blind, placebo run in trial of sertraline N=15, Grade C
Fluoxetine 60 mg/ day for 90 days ⁴⁵	Diffuse (involved prefrontal cortex)	Chronic	Neuropsychiatric: • OCD (due to TBI) improved	Case study N=1, Grade D
Paroxetine 10-40 mg Citalopram 10-40 mg ⁴⁷	Left, right, bilateral lesions via stroke, hypoxia, TBI	N/A	Neurobehavioural: • pathological crying improved; both drugs equally effective	No placebo given N=26, Grade D

SSRI = selective serotonin reuptake inhibitors; MVA = motor vehicle accident; N/A= not available; OCD = obsessive-compulsive disorder

amitriptyline with 50-75 mg of desipramine.⁴³ This combination had beneficial effects on patients’ verbalisation and arousal (Grade D).

Selective serotonin reuptake inhibitors

Evidence for the role of SSRIs in the treatment of brain injuries is summarized in Table 3. Selective serotonin reuptake inhibitors appear useful in either the acute or chronic setting, where the location of the lesion does not appear to be linked to management. The majority of studies suggest that SSRIs

improve NC, NP, and NBH deficits, specifically, agitation, depression, psychomotor retardation and recent memory loss. The evidence is not robust however, with most data coming from nonrandomized trials.

Two studies looked at the use of sertraline, at an average dose of 100 mg/day.^{19,44} In one study the treatment was only continued for two weeks and it failed to show any benefits (Grade C).¹⁹ In the second study the treatment was continued for eight weeks.⁴⁴ Sertraline was found to be beneficial in the control of agitation,

Table 4: Amantadine and its role in brain injury

Amantadine Dose	Lesion	Time (acute<1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
200 mg ⁴⁸	Diffuse	Acute	1) Neurocognitive: (specifics N/A) 2) Neurobehavioural: (specifics N/A) • no change in memory	Double blind placebo controlled randomized crossover N=35, Grade B
50-200 mg ⁴⁹	Diffuse	Acute-chronic	1) Neurocognitive: • attention, concentration, alertness, arousal, and mobility improved 2) Neurobehavioural: • agitation and anxiety improved • no change in memory, or sexual inappropriateness	Retrospective analysis N=12, Grade D
100 mg tid ⁵⁰	Subarachnoid and intra-ventricular hemorrhage	Chronic	Neurobehavioural: • increased motivation and decreased apathy	Double blind, placebo-controlled N=1, Grade C
150 mg bid ²⁰	Contusion, cerebral hemorrhage	N/A	• No benefits in comparison to placebo	Prospective randomized, double blind placebo controlled crossover design N=10, Grade B
100 mg ²	Large left subdural hematoma	Chronic	N/A	Case study with ABAB design, Grade D
400 mg and sinemet 25/100 tid ⁵¹	Frontal lobe lesion	Chronic	Neurobehavioural/Neurocognitive: • decreased impulsivity and perseveration; improved executive functioning	Case study, Grade D

N/A= not available; tid = three times daily; bid = twice daily

and it also improved patients' psychomotor speed, recent memory and depressed mood (Grade C).

Fluoxetine at a dose of 60 mg/day for three months was shown to be effective in the treatment of obsessive-compulsive disorder caused by brain injury (Grade D).⁴⁵ Another study found a combination of 20 mg/day of citalopram and 600 mg/day of carbamazepine to have beneficial effects on major depression, anxiety, disorganization and psychomotor slowness (Grade D).⁴⁶ Finally, one study has shown that either paroxetine or citalopram given at a dose of 10-40 mg/day to be equally effective in the treatment of pathological crying (Grade D).⁴⁷ None of the studies addressed LOC.

Amantadine

The studies of amantadine (Table 4) indicate that it is beneficial in either the acute or chronic care setting, where the lesion can be diffuse, frontal, or right sided. Main indications include managing NC or NBH deficits resulting from brain injury. In five studies the daily dose of amantadine was between 100 and 300 mg.^{2,20,48,49,50}

One study reported that treatment with amantadine showed no benefit (Grade B).²⁰

A single study showed an improvement in motivation and a decreased level of apathy associated with treatment (Grade C).⁵⁰

Two studies have shown amantadine to produce both NC benefits, namely improvements in attention, concentration, alertness, as well as improvements in such NBH problems as

agitation and anxiety.^{48,49} These studies were not of uniform quality however (Grade B and D, respectively). Both studies indicated that there was no improvement in memory.

An improvement in the level of consciousness was displayed with amantadine treatment in two studies (both Grade D).^{2,49} A separate study, combining 400 mg of amantadine with 25/100 sinemet showed a decrease in impulsivity and perseveration as well as improved executive functioning (Grade D).⁵¹ None of the studies to date have shown an increase in memory.

Bromocriptine

The studies that investigated the role of bromocriptine in the treatment of brain injury are summarised in Table 5. Bromocriptine appears to be beneficial in chronic head injury settings, where the patient's head injury is diffuse in nature, involving especially bifrontal, left sided or brainstem lesions (pons and midbrain). The main indicators to use bromocriptine would be to treat a vegetative, akinetic mutism, or minimal conscious state in a chronic care setting.

Three similar studies looked at the use of bromocriptine in circumstances contiguous with the above description. One used a dose of 10-40 mg of bromocriptine and showed improvements in akinetic mutism (Grade D).^{52,53} Another used 5 mg with sensory stimulation and displayed improvements in patients with vegetative/minimal consciousness LOC (Grade B).⁵⁴ The third combined 100 mg of bromocriptine with 100 mg of ephedrine and showed improvements in akinetic mutism (Grade D).⁵⁵

Table 5. Bromocriptine and its role in brain injury

Bromocriptine Dose	Lesion	Time (acute<1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
5 mg with sensory stimulation ⁵⁴	Unspecified	Acute to chronic	N/A	Retrospective review, N=75, Grade B
100 mg with ephedrine ⁵²	cephalus global	Obstructive hydro-	Chronic	N/A Case study, Grade D
10-40 mg ⁵²	Brainstem lesions, left sided lesions	Chronic	N/A	3 case studies, Grade D
2.5 mg ⁵⁵	Varied	Chronic	Neurocognitive: • executive control, linked to prefrontal regions, improved	Double blind placebo control crossover N=24, Grade B
7.5-15 mg ⁵⁶	Bifrontal Small R parietal	Chronic	Neurobehavioural: • akathisia improved	1 case, Grade D

Table 6: L-dopa and its role in brain injury

L-dopa Dose	Lesion	Time (acute<1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
25/250 x4/day ⁵⁸	N/A	Chronic	N/A	Case study ABAB design, Grade D
1) 25/100 x 7/day 2) l-dopa: 10/100 x5/day bromocriptine 7.5 mg/day ⁵⁷	1) Diffuse, right temporal contusion	Chronic	N/A N=2, Grade D	Case study
25/250 x 4/day ⁵⁹	Right subdural hematoma and subarachnoid hemorrhages	Chronic	N/A	Case study N=1, Grade D
l-dopa 25/200 tid Amantadine 250 mg Bromocriptine 5 mg bid ⁶⁰	Bilateral frontal traumatic lesions	Chronic	Neurocognitive: • affect, initiation, speech, dysarthria and ataxia, improved • increased agitation	Case study N=1, Grade D

Dosage regimens cited as carbidopa (mg)/levodopa (mg)

Two further studies using bromocriptine suggested benefits in the NC and NBH realms. One managed to demonstrate that a low dose of bromocriptine (2.5 mg) improved executive control (Grade B).⁵⁵ The second showed bromocriptine to be beneficial in the treatment of akathisia (Grade D).⁵⁶

L-dopa

The studies that investigated the potential of l-dopa in the treatment of brain injury are listed in Table 6. Evidence from nonrandomized studies suggests that l-dopa might be useful in a chronic brain injury care setting where the lesion is not necessarily specific to a single location. The main indication for use would be a persistent vegetative state. The doses of l-dopa used for this purpose ranged from 10/100 for five days⁵⁷ to 25/100 for seven days⁵⁷ and 25/250 for four days^{58,59} (all Grade D). It appears that l-dopa alone may or may not treat coma (mixed results). Neuropsychiatric difficulties improved in one study in which 25/200 of l-dopa three times a day was combined

with 250 mg of amantadine and 5 mg of bromocriptine twice a day (Grade D).⁶⁰

Valproic acid

The studies of valproic acid (Table 7) suggest a beneficial role in the chronic setting of lesions that are not specific to any region. Main indications to use valproic acid include NP, NBH and NC deficits that affect agitation, rather than any mood disorders.

One controlled trial also indicated a negative impact of valproic acid treatment on decision making speed (Grade A).⁶¹

It is also worth noting that one study displayed an increased mortality with valproic acid use (Grade B).⁶²

Generally, of the five studies that looked at the use of valproic acid^{22,61-64} the dose used varied between 600 and 2250 mg/day and serum levels ranged from 40 to 100 μ/ml. Two studies reported positive NC effects, including improvement in recent memory and problem solving (Grade D and A, respectively).^{22,61}

Table 7: Valproic acid and its role in brain injury

Valproic Acid Dose	Lesion	Time (acute<1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
40-100ug/ml serum concentration ⁶²	N/A	Acute-Chronic	<ul style="list-style-type: none"> • Did not prevent post-traumatic seizures • No positive effects on cognition • Increase mortality • Neuropsychiatric side effects were benign 	Randomized, double-masked, parallel group clinical trial N=279, Grade B
600-1000 mg/d ⁶¹	N/A	N/A	Neurocognitive: <ul style="list-style-type: none"> • recent memory improved • decision making speed diminished • no change in mood 	Literature Review, Grade A
750 mg/day-2250 mg/day serum 35-100 µg/ml ²²	#1 Right subdural haematoma and diffuse, right frontal temporal area #2 bifrontal, left occipital, diffuse #3: left fronto-temporal atrophy #4 right cerebellum #5 bifrontal, diffuse	Chronic	1) Neurobehavioural: <ul style="list-style-type: none"> • destructive/aggressive behaviour and restlessness improved 2) Neuropsychiatric: <ul style="list-style-type: none"> • depression and mania improved 3) Neurocognitive: <ul style="list-style-type: none"> • problem solving improved 	Case study N=5, Grade D
1250 mg/day ⁶³	N/A	Chronic	Neurobehavioural: <ul style="list-style-type: none"> • disinhibition, impulsivity, lability, and alertness improved 	Case series n=29, Grade D
1818 mg ± 791 mg/day serum 85.6 ± 29.6 ug/ml ⁶⁴	N/A	Chronic	Neurobehavioural (specifics N/A)	Retrospective chart review n=11, Grade D

Table 8: Modafinil and its role in brain injury

Modafinil Dose	Lesion	Time (acute<1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
200 mg bid ⁶⁵	Alcoholic organic brain syndrome (frontal and cortical)	Chronic	Neurocognitive: <ul style="list-style-type: none"> • memory, psychomotor activity, and intellectual function improved 	Double blind, placebo control study N= 40, Grade B
100-400 mg for 5-13 months ⁶⁶	Unknown	N/A	Neurocognitive: <ul style="list-style-type: none"> • attention improved 	Cohort N=10, Grade C

Three reports suggest that valproic acid treatment helped with such NBH symptoms as destructive and aggressive behaviour, restlessness, disinhibition, impulsivity, lability and alertness (all Grade D).^{22,63,64} Another study of similar quality indicated a positive effect of valproic acid treatment on depression and mania (Grade D).²²

Valproic acid did not affect LOC.

Modafinil

The evidence for the role of modafinil in the treatment of brain injuries is summarised in Table 8. Modafinil appears to be useful in the chronic setting. It is unknown if the location of the lesion plays an important role in management. The two studies

that investigated the role of modafinil showed that a dose between 100 and 400 mg improved NC deficits, specifically memory, attention, and it improved daytime somnolence (Grade B and D, respectively).^{65,66}

Hyperbaric oxygen therapy

The scientific literature does not currently support the use of hyperbaric oxygen in the treatment of TBI.⁶⁷ The studies that have shown it beneficial (Table 9) suggest that its main indication for use is chronic minimal consciousness, or acute coma due to carbon monoxide poisoning. In terms of chronic TBI management, the lesion site does not appear to be important. In one study²⁴ the oxygen therapy was given every eight hours

for one hour at 1.5 atmospheres with an average of 21 treatments. This kind of therapy resulted in decreased mortality at 12 months, but no improvement in the quality of life (Grade B). Also of note for this treatment modality is the risk of seizures.⁶⁷ This is a rare occurrence, but can be quite dramatic.

Electroconvulsive therapy

The investigations of ECT as a modality used for the treatment of brain injuries are displayed in Table 10. Electroconvulsive therapy may prove to be useful in a chronic setting, where the type of lesion is not important, with respect to management. The main indications to use ECT would be to treat NP and NBH deficits, especially depression (Grade D).⁷⁴ It appears that ECT does not cause any decline in cognition, but there are no indications that there is any improvement of neurocognition.

Other agents

The limited studies on the effects of TMS, lactate and bupropion in the treatment of brain injuries are listed in Table

11. It appears that TMS administered in 30-minute bursts once per week for eight weeks can help to treat depression (Grade D).⁷⁵ Lactate improves cognitive ability (in rats),²⁸ and bupropion at 150 mg/day¹⁸ is useful in treating restlessness (both Grade D). Unfortunately, due to the limited number of studies uncertainty still exists about the optimal time to introduce these agents, and whether or not the location of the lesion is significant.

DISCUSSION

Neuropsychiatric Deficits

The only agents which were effective for NP disorders were SSRIs, valproic acid, ECT and TMS. Selective serotonin reuptake inhibitors provided the best source for alleviating acute or chronic mood disorders, specifically major depression. Treating depression early allows for greater response and avoids a possible worsening of symptoms, which also relate to NC deficits⁴⁶ – particularly since patients with depression and TBI

Table 9: Hyperbaric oxygen therapy and its role in brain injury

Hyperbaric oxygen Dose	Lesion	Time (acute<1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
Monoplace chamber every 8 hours for 1 hour 1.5 atm absolute for 2 weeks (average 21 treatments) ²⁴	N/A	Acute	Mortality: • decreased at 12 months, but no further increase in quality of life for those that survived	Prospective randomized trial N=168, Grade B
2.4 ATA for 90 min bid for 3 days ⁶⁷	Bilateral cerebral dysfunction: via CO poisoning	Acute	N/A	Case study N=1, Grade D
Unknown amount ⁶⁸	N/A	Chronic	N/A	Randomized control trial N=35, Grade B

CO = carbon monoxide; NA= not available; bid = twice daily; atm = atmospheres; ATA = atmosphere absolutes

Table 10: Electroconvulsive therapy (ECT) and its role in brain injury

ECT Dose	Lesion	Time (acute <1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
ECT ⁶⁹	Gunshot/ cerebral cortical laceration	Acute	Neuropsychiatric: • depression improved	Case study N=1, Grade D
ECT ⁷⁰	Diffuse	Chronic	Neuropsychiatric: • major depression improved	Case study N=2, Grade D
ECT ⁷¹	Gunshot/ diffuse	Chronic	Neuropsychiatric: • depression improved	Case study N=1, Grade D
ECT ⁷²	Bilateral frontal, left thalamic contusions	Chronic	Neurobehavioural: • agitation improved • increased response to medications also noted	Case study N=1, Grade D
ECT ⁷³	N/A	Chronic	Neuropsychiatric: (specifics N/A) • no cognitive side effects	N=11, Grade D

Table 11: Review of the role of TMS, lactate, bupropion in brain injury

Other agents Dose	Lesion	Time (acute <1month)	Condition Treated and Treatment Results	Study Design/Grade of Recommendation
TMS: 30 min burst firing/week for 5weeks ⁷⁴	Hippocampal-amygdaloid	N/A	Neuropsychiatric: • depression and phobia improved	N=4, Grade D
Lactate Infusion, 3hrs, 65ml/hr ²⁸	Moderate brain injury (rats)	Acute (30min)	Neurocognitive: (specifics N/A)	Laboratory Animal Study, Grade D
Bupropion; 150 mg/day ¹⁸	Right temporal haematoma	Chronic	Neurobehavioural: • restlessness improved	Case study, N=1, Grade D

relate their cognitive difficulties to the TBI rather than the depression.⁴⁴

In terms of NBH deficits, disinhibition, agitation, anger and irritability have been frequently identified as accompanying symptoms of depression following TBI.⁷⁶ These behavioural problems further isolate the individual, and worsen the depression. Fortunately, SSRIs have been found to treat these symptoms as well, which may help with psychosocial functioning, and directly impact quality of life. Interesting or unusual conclusions suggested from the evidence include the induction of akathisia precipitated by sertraline, and the possible success in treating obsessive-compulsive disorder (OCD), and pathological crying after a brain injury.^{45,52}

When SSRIs and other agents such as methylphenidate are unable to treat longstanding depression, the best alternative is ECT. Electroconvulsive therapy was found to benefit chronic depression and was shown not to cause any further decline in cognition. Even though valproic acid has been found to be useful in treating mood disorders (including mania), one study has shown an increase in mortality with this agent.⁶²

Neurocognitive Deficits

Numerous agents have been found useful in treating NC deficits. As discussed earlier, SSRIs have shown some NC benefits, although the etiology of the deficits may arise from the depression. This may be a partial explanation as to why SSRIs are not useful in dealing with acute cognitive deficits, as acute cognitive deficits would be less likely to correspond to a depression. The evidence reveals, however, that sertraline does not show any benefits in the acute setting, while citalopram with carbamazepine does show benefits. The different results may simply be attributed to the different SSRIs or the addition of mood stabilizer.

Methylphenidate was the only agent to show consistent cognitive benefits (attention and processing speed) in the acute setting. Methylphenidate also showed benefits in the chronic setting as well, however the type of cognitive benefits differed. In the chronic state, methylphenidate improved processing speed, but there were mixed results in terms of improvement in attention. It is interesting to note that methylphenidate was shown to improve memory.

Modafinil was another agent that demonstrated improved chronic cognitive benefits. However, unlike methylphenidate, modafinil improved memory and attention along with increasing

arousal and psychomotor functioning. The increase in arousal is not surprising since modafinil is used to treat narcolepsy. Modafinil may be the best agent in treating chronic neurocognitive deficits; however, no study specifically indicates modafinil's use in the acute setting.

Amantadine, l-dopa, and lactate are also useful in managing neurocognitive deficits. Amantadine appears to have effects both acutely and chronically, affecting attention, concentration, alertness, arousal and mobility. There does not appear to be a clear lesion that amantadine is most useful for. L-dopa, on the other hand, appears to be useful with bilateral frontal traumatic lesions, specifically. It helps with affect, initiation, speech, dysarthria and ataxia, but often leads to increased agitation. The case study examining this also used amantadine and bromocriptine in unison with l-dopa to achieve this effect. It is suggested that lactate is helpful in NC deficits; however, the study that supports this used rats as subjects and is, therefore, of limited use.

Neurobehavioural

Agitation is the most pervasive symptom in TBI and one of the largest obstacles in providing necessary treatment. Neurobehavioural deficits also include anxiety, restlessness and poor impulse control. Fortunately, there are numerous agents that deal with NBH deficits. As discussed earlier, SSRIs play a role in NBH deficits, specifically anxiety and agitation; however, their role in the acute setting is more controversial, as one study showed no benefits. Amantadine was the only agent that did show consistent NBH improvement in terms of anxiety and agitation.

In managing chronic NBH deficits, benefits should be thought of as affecting either agitation or restlessness. Methylphenidate, amitriptyline, SSRIs and ECT all are found to be beneficial in responding to chronic agitation. It is worth noting that SSRIs also improve chronic anxiety. In terms of restlessness, bromocriptine, bupropion and valproic acid have all been found to be beneficial. It appears that of all the agents, valproic acid shows the largest breadth of reducing both restlessness and agitation along with impulsivity. As mentioned earlier, in one large study, valproic acid has been linked with increasing mortality and only showed minimal benefits. Thus, in dealing with chronic agitation, methylphenidate, SSRIs or amitriptyline can be used, with ECT being the last resort. In dealing with restlessness, bromocriptine or bupropion may be useful, with valproic acid being the last resort.

Table 12: Summary of agents and optimal clinical scenario use

	Neuropsychiatric symptoms (mood)	Neurocognitive deficits	Neurobehavioural deficits	Level of consciousness
ACUTE (<1month)	SSRI ECT	Methylphenidate (attn, speed) ±SSRI (motor, speed, org, recent memory) Amantadine (attn, concentration, alertness, arousal, mobility)	Amantadine (agitation, anxiety) ±SSRI (anxiety)	Bromocriptine (veg, am) Methylphenidate (coma, min) Hyperbaric oxy (coma, min)
CHRONIC (>1month)	SSRI (OCD, pathological crying) ECT Valproic acid TMS (phobia)	Modafinil: (memory, motor, attn, arousal) Methylphenidate (speed, memory, ±attn) SSRI (motor, speed, recent memory, org) Amantadine (attn, concentration, alertness, arousal, mobility) *±Valproic acid: (problem solving, recent memory) Bromocriptine (org) **Lactate (specifics unknown) **L-dopa with amantadine, bromocriptine (affect, initiation, speech, dysarthria)	Methylphenidate (agitation, impulse) Amitriptyline (agitation) SSRI (anxiety, agitation) ECT (agitation) Amantadine (agitation, anxiety, motivation, apathy) *Valproic Acid: (agitation, impulse, restlessness) Bromocriptine: (restlessness) **Bupropion (restlessness)	Bromocriptine (am, veg) L-dopa (veg, ±coma) Amitriptyline (min) Hyperbaric oxygen (min, coma) Amantadine (min)

Oxy = oxygen, min = minimal consciousness, veg = vegetative state, am = akinetic mutism, OCD = obsessive-compulsive disorder, attn=attention, org = organization

Level of consciousness – arousal

The only agents that did not effectively increase LOC were SSRIs, valproic acid, ECT, TMS, lactate infusion, and bupropion. Bromocriptine and hyperbaric oxygen therapy are both beneficial in acute and chronic conditions. Bromocriptine, however, can be used in wide variety of states of decreased consciousness, such as persistent vegetative state, akinetic mutism, and minimal consciousness. Additionally, bromocriptine appears to have a special sensitivity for treating akinetic mutism (bromocriptine is a D2 receptor agonist, and D2 receptors are found in areas of speech).⁵² Oxygen therapy, on the other hand, appears to be more useful for more poison induced comas in the acute setting and minimal consciousness in the chronic setting. Along with bromocriptine and hyperbaric oxygen, amitriptyline has been found useful in dealing with patients with chronic minimal consciousness.

Methylphenidate and L-dopa are useful in acute and chronic coma, respectively. L-dopa was found to be useful in chronic coma and persistent vegetative state. This would suggest that this drug is best suited for the deepest and most longstanding loss of consciousness. Methylphenidate, on the other hand, was found to be useful in treating both an acute coma and minimal consciousness.

SUMMARY OF AGENTS

Upon reviewing the evidence for a variety of pharmacological agents in the setting of brain injury, it appears that there is

evidence for the usage of certain agents in particular clinical scenarios. Timing and quality of symptoms, along with the timing of agent administration, are all relevant factors for determining the usage of any given agent. A summary of these agents can be seen in Table 12. Methylphenidate can be used in an acute treatment of low LOC. Bromocriptine and hyperbaric oxygen appear to be effective in the treatment of acute and chronic low LOC, while amitriptyline and amantadine have shown to be effective in treating chronic low LOC, only. Selective serotonin reuptake inhibitors and ECT can be effective in the treatment of both acute and chronic mood symptoms. Valproic acid and TMS can also be helpful in the treatment of chronic NP symptoms. The evidence gathered to date also suggests that methylphenidate and amantadine can be used to treat certain NC deficits in an acute setting. Modafinil, methylphenidate, SSRIs, amantadine, and valproic acid, as well as bromocriptine and L-dopa, can be used to treat various NC deficits in chronic setting. Finally, amantadine and SSRIs can be used to treat anxiety in an acute setting. Methylphenidate, amitriptyline, SSRIs, ECT, amantadine, valproic acid, bromocriptine and bupropion can be used for various NBH deficits in a chronic setting.

LIMITATIONS

There were a number of limitations to this review. A number of them involved the lack of precision with a variety of definitions and terms. For example, no timelines were provided

with regard to symptom resolution; from a clinical standpoint, this could have ensured that an agent had been allowed sufficient opportunity to be effective before being discontinued. Most case studies noticed improvements within seven days, and it was this acute improvement that linked the agent with the improving symptom. The LOC was never defined accurately prior to intervention. This could have been achieved by stating the Glasgow Coma Scale or the Rancho Los Amigo Scale score. The initial brain lesion that the patient had on arrival to hospital was never recorded, only the most recent lesion prior to intervention was recorded. There may be a correlation with the location of the lesion and the agent used to treat the symptoms. While the intervention medication was recorded, the patient was often taking numerous medications at the time of the recovery of symptoms. It may have been more useful to record all the medications and their levels in order to examine effects of polypharmacy. Each study was weighted equally, although not all studies were of equal quality. Different study designs and different sample sizes influence the appropriateness and validity of each study. While the grade of evidence found in each paper is identified, a majority of the evidence found to date has been of insufficient quality to make recommendations for routine usage of certain treatment modalities.

The strongest limitation of this literature review is that the individual studies used different tests/assessment methods to determine the effect of a certain drug on a particular symptom. These tests do not all share the same sensitivity or specificity; thus, what is a significant difference in one study may not be significant in another. Also, not all studies took into account that the measurement tool may show a significant improvement of a symptom, but that functionally the patient did not improve. The studies under review did not all share the same inclusion and exclusion criteria; thus the study population was heterogeneous. It is worth noting that most studies excluded patients with previous psychiatric diagnoses.

These studies are not exhaustive and our search did not include additional medications such as neuroleptics, cognitive enhancers, beta-blockers, benzodiazepines, and azospirones. Numerous studies did not define the LOC of the patient, defining the symptom of interest. For instance, many studies did not use coma, akinetic mutism or minimal consciousness to define a patient's state of arousal; the clinical picture that was provided inferred these states. Many studies did not clearly describe or quantify agitation states. This is important because it was unclear if the author distinguished this feature from restlessness, or if a patient was having a delirious episode.

Much of the evidence reviewed was poor and sometimes even conflicting. More precise findings require testing in rigorous prospective trials.

SUMMARY

The main purpose of this review was to make readers aware of the vast amount of pharmacological agents that are available to clinicians to manage the various consequences of a head injury. The evidence gathered to date suggests that a number of pharmacological and nonpharmacological interventions have a role in the treatment of decreased levels of consciousness and the neurocognitive, neuropsychiatric and NBH deficits resulting from brain injury. After reviewing articles pertaining to treatment

of brain injuries, there is evidence for the usage of certain pharmacological interventions in particular clinical settings. These conclusions, however, are not definitive. There is no strong evidence for recommending optimal treatment guidelines. The evidence suggests that each case should be treated separately and clinicians should become more rigorous in regard to recording the neurological deficits they are attempting to treat. We hope that this review can initiate future studies and add to the care of head injured patients' numerous neurological deficits.

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