The impact of pharmacological treatments on outcome after adult traumatic brain injury: What does the research show?

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Abstract

A traumatic brain injury (TBI) can cause immediate and delayed damage to the brain producing long-term cognitive and behavioural problems. Young people in the early stages of a productive life are at most risk of sustaining a TBI making these persistent problems of major personal and social importance. Post-TBI rehabilitation provides one possible strategy for improving outcome following injury. Pharmacological treatments, on the other hand, have the potential to either minimise the amount of damage that the brain sustains following TBI, thereby improving outcome, or reduce persistent biochemical disruptions that are associated with poorer outcome. However, research in this area has shown mixed results hampering advances in the treatment of this condition. This thesis will, therefore, synthesise the findings from pre-clinical and clinical research that has examined the effects of pharmacological treatments on cognitive and behavioural outcome following adult TBI.

A large number of the pharmacological agents have been investigated in pre-clinical experimental research with rodents making it difficult to consolidate the findings. Therefore, the first study meta-analysed the data from 223 pre-clinical studies that examined 91 pharmacological treatments in adult male rodents (rats, mice) after TBI. Sixteen treatments improved cognition and motor outcome across a range of models of TBI injury. Four of these showed dose-dependent treatment effects and two showed treatment-interval effects. The findings suggest that anti-inflammatories are the most efficacious treatments for improving cognition and motor function in rodents following TBI. Behaviour, on the other hand, did not improve with any of the treatments.

It is unclear whether these treatment benefits translate to an adult human TBI population. Study two, therefore, evaluated the impact of early (≤ 7 days post-injury) pharmacological treatments on cognition and behaviour in humans after TBI using meta-analytic techniques. Twenty-two studies that investigated eleven different treatments were analysed. Two treatments (amantadine and bradycor) showed marked improvements in arousal. A further three were associated with dose-dependent treatment effects (LF 16-0687Ms, dexanabinol, GK-11). The outcome measure used to evaluate a pharmacological agent influenced the likelihood of finding a treatment benefit.

It is also unclear whether long-term changes (≥ 4 weeks post-injury) to neurotransmitters in the brain additionally benefit from pharmacological interventions. Again, the findings from clinical studies in an adult human TBI population have been inconsistent. In study three, the data from 30 studies that investigated 19 pharmacological treatments administered prior to and spanning, the post-acute stage, and in the post-acute stage after adult human TBI were synthesised. Three treatments (methylphenidate, amantadine, donepezil) improved behaviour (mood, combativeness), cognition or general outcome while one (sertraline) worsened post-concussion symptoms and cognition.

In summary, this thesis confirms that both early and post-acute pharmacological interventions can improve the outcomes of adult rodents and humans after TBI. Early treatments that reduce brain swelling (i.e., inflammation and oedema) appear to be beneficial to outcome in both rodents and humans. Stimulant treatments administered to humans in the early and post-acute stage after TBI also show marked benefits. Finally, drug dosage, injury-to-treatment interval and outcome measure influenced the likelihood of finding treatment benefits.

Declaration

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*Published Works

Wheaton, P., Mathias, J.L., Vink, R. Impact of pharmacological treatments on outcome in adult rodents after traumatic brain injury: A meta-analysis. *Journal of Psychopharmacology*. (In Press)

In accordance with publisher guidelines a link to this paper is provided at the beginning of Chapter 3.

Wheaton, P., Mathias, J.L., Vink, R. (2009). Impact of early pharmacological treatment on cognitive and behavioral outcome after traumatic brain injury in adults: A meta-analysis. *Journal of Clinical Psychopharmacology, 29(5)*. 468-477.

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Wheaton, P., Mathias, J.L., Vink, R. Impact of pharmacological treatments on cognitive and behavioural outcome in the post-acute stages of adult traumatic brain injury: A meta-analysis. Manuscript submitted for publication. (Under Review).

The abovementioned studies are presented in Chapters 3, 4, and 5, respectively. These papers were originally prepared to meet different journal requirements. To

ensure consistency in the presentation of this thesis the bibliographic style of the American Psychological Association, sixth edition publication manual (Americal Psychological Association, 2009) has been used and the original English spelling has been retained. Accordingly, chapters may vary slightly from the published versions. Every attempt was made to avoid a repetition of the wording in the method section, however, similarity in the procedures that were used meant that some duplication was unavoidable.

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Statements of the contributions on jointly authored papers

Chapter 3

Title: Impact of pharmacological treatments on outcome in adult rodents after traumatic brain injury: A meta-analysis.

Co-Authors: J.L. Mathias, R. Vink

Contributions: Both co-authors acted in a supervisory capacity during all stages of the research and manuscript preparation. I was responsible for the study's inception and design, data-collection, statistical analyses, data interpretation, and manuscript preparation, under the supervision of J.L. Mathias and R. Vink.

Chapter 4

Title: Impact of early pharmacological treatment on cognitive and behavioural outcome after traumatic brain injury in adults: A meta-analysis.

Co-Authors: J.L. Mathias, R. Vink

Contributions: Both co-authors acted in a supervisory capacity during all stages of the research and manuscript preparation. I was responsible for the study's inception and design, data-collection, statistical analyses, data interpretation, and manuscript preparation, under the supervision of J.L. Mathias and R. Vink.

Chapter 5

Title: Impact of pharmacological treatments on cognitive and behavioural outcome in the post-acute stage of adult traumatic brain injury: A comparison of treatment effects.

Co-Authors: J.L. Mathias, R. Vink

Contributions: Both co-authors acted in a supervisory capacity during all stages of the research and manuscript preparation. I was responsible for the study's inception and design, data-collection, statistical analyses, data interpretation, and manuscript preparation, under the supervision of J.L. Mathias and R. Vink.

The undersigned agree that the statements made regarding author contributions are accurate and true.

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J.L. Mathias Date

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List of Abbreviations

AMPA	a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic
APP	amyloid precursor protein
ATP	adenosine triphosphate
Bcl	B-cell lymphoma
BDNF	brain derived neurotrophic factor
BBB	blood brain barrier
CCI	controlled cortical impact injury
ChAT	choline acetyl transferase
DAI	diffuse axonal injury
DNA	deoxyribonucleic acid
FPI	fluid percussion injury
GABA	*y*-aminobutyric acid
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
ICAM	intercellular adhesion molecule
ICP	intracranial pressure
IgG	nonspecific control antibody
IL	interleukin
IQ	intelligence quotient
LOC	loss of consciousness
mGluR	metabotropic
NGF	nerve growth factor
NMDA	N-methyl-D-aspartate
NOS	nitric oxide synthase

PARP	poly(ADP-ribose) polymerase
PPAR	peroxisome proliferator-activated receptor
PTA	post-traumatic amnesia
sAPP	soluble amyloid precursor protein
TBI	traumatic brain injury
TGF	transforming growth factor
TNF	tumor necrosis factor
TRH	thyrotropin releasing hormone
VCAM	vascular cell adhesion molecule
WD	weight drop injury

Chapter 1: Introduction

The Scope and Focus of the Thesis

Traumatic brain injuries (TBIs) are a leading cause of mortality and morbidity in adults (Engel, Slemmer, Vlug, Maas, & Weber, 2005; Javouhey, Guerin, & Chiron, 2006; Marsh & Sleigh, 2002). Although improved medical management immediately following injury has reduced mortality rates, TBI remains a major source of long-term disability in survivors (Javouhey, et al., 2006; Kaufman, et al., 2006; Marsh & Sleigh, 2002; Rassovsky, et al., 2006b). Accordingly, the development of effective therapeutic interventions to reduce the cognitive and behavioural problems that result from a TBI is of major social, economic and public health importance (Dieli, 2002; Guha, 2004; Lee, Lyketsos, & Rao, 2003; Marsh & Sleigh, 2002; Mendez, Corbett, Macias, & Laptook, 2005; Tolias & Bullock, 2004).

Pharmacological treatments, which target the biochemical changes that typically occur following TBI, represent a promising therapeutic strategy to reduce the cognitive and behavioural problems caused by these injuries. The safety and efficacy of these interventions are primarily examined in rodent models of human TBI, prior to their use in a clinical TBI population (Finnie, 2001). However, while a number of these treatments have shown success in reducing cognitive and behavioural impairments in rodents after TBI, these benefits have not always carried over to clinical trials (Faden, 2001; Faden, et al., 2001; Narayan, Michel, & Group, 2002), challenging the validity of rodent models in understanding human TBI (Faden, 2001; Faden, et al. 2001; Macleod, O'Collins, Howells, & Donnan, 2004). One explanation for inconsistencies in the findings from rodent and human research is that there are methodological differences between the two species. For example, the success of pharmacological treatments in experimental studies may not carry over to clinical trials in humans because the controlled experimental injuries administered to rodents fail to replicate the complex nature of human TBI (Narayan, et al. 2002).

In addition, conflicting findings from clinical trials regarding the most effective treatments for reducing cognitive and behavioural problems have hindered advances in the treatment of this condition. A number of factors may contribute to these discrepant findings. Firstly, treatment outcomes may be influenced by the severity of injury and the time post-injury that treatment is, or can be, initiated (Faden, 2001; Faden, et al. 2001; Glenn & Wroblewski, 2005). There are also difficulties inherent in conducting clinical trials with humans that have sustained a TBI, including the fact that these individuals have an increased risk of developing severe drug-related side effects (e.g., nausea, psychosis, agitation) which may also need to be considered (Arciniegas, Topkoff, & Silver, 2000; Kaye, Townsend, & Ivins, 2003; Rao, Jellinek, & Woolston, 1985; Rao & Lyketsos, 2000). Small sample sizes are also common in human research, which limits the power of clinical trials to detect a significant treatment effect (Freedman & Bernstein, 1999). Finally, alterations to the metabolic state of the brain as a result of pre-injury substance use (e.g., alcohol) may complicate recovery by aggravating the amount of damage that the brain sustains (Altura & Altura, 1999), which may negatively impact on cognitive and behavioural outcome and the efficacy of pharmacological interventions.

To date, a very large number of experimental studies and clinical trials have examined the impact of a variety of pharmacological agents on cognitive and behavioural outcome following TBI. However, it is difficult for clinicians and researchers to synthesise and integrate this research in order to evaluate the relative efficacy of these treatments. Quantitative reviews of rodent and human research that examine post-injury pharmacological treatments are therefore needed. This thesis, therefore, examined the impact of pharmacological treatments in adult rodents and humans after a traumatic brain injury (TBI) in order to identify those treatments that are the most efficacious in reducing cognitive and

behavioural problems following injury and some of the methodological variables (i.e. injury severity, treatment interval, drug dosage) that may impact on treatment efficacy.

Chapter 1 presents a contextual framework for the current research by providing a review of TBI and its impact on cognitive and behavioural outcome. Chapter 2 focuses on the pathology of TBI, with particular emphasis on the secondary biochemical changes that occur soon after injury, together with a brief overview of the different pharmacological treatments that have been used to treat cognitive and behavioural problems following injury and their mechanisms of action. This chapter concludes with a summary and statement of the research aims.

1.1 Traumatic Brain Injury

A traumatic brain injury (TBI) includes an acute injury in which an external force impacts with the skull, damaging the brain, altering consciousness, and resulting in transient or permanent neuropsychological impairments (Comper, Bisschop, Carnide, & Tricco, 2005). The latter impairments may include cognitive deficits (e.g., attention, memory, executive function) (Jorge, 2005; Napolitano, Elovic, & Qureshi, 2005), motor impairments (Brauer, Broome, Stone, Clewett, & Herzig, 2004; Marion, 1999) and affective disorders, such as depression and personality changes (Jorge, 2005; Napolitano, et al., 2005). The amount of energy that is translated to the brain at the time of injury determines the severity of injury, with more severe injuries associated with greater damage to neural tissue and poorer outcome (Garnett, Blamire, Rajogopalan, Styles, & Cadoux-Hudson, 2000; Marino, et al., 2007).

1.1.1 Prevalence, risk factors and causes of TBI

It is estimated that up to 200 in every 100,000 people, will be hospitalised as a result of a TBI each year (Marion, 1999; Narayan, et al. 2002). However, prevalence estimates show considerable variability, with worldwide estimates ranging from 149 per 100,000 people in Australia (Fortune & Wen, 1999) to an extremely high 1,967 per 100,000 people in Scotland (Comper, et al. 2005). In addition, these figures are likely to underestimate the true incidence of TBI due to errors in the coding of these injuries (Jennett, 1996) and the fact that many individuals who have sustained a mild TBI neither seek medical attention or require hospitalisation following their injury (Dieli, 2002; Khan, Baguley, & Cameron, 2003).

For individuals who have experienced a TBI, it is estimated that between 5% (Baguley, Slewa-Younan, Lazarus, & Green, 2000; Harris, DiRusso, Sullivan, & Benzil, 2003) and 30% (Harris, et al. 2003) will die as a result of their injuries and up to 6% will be left with long-term or permanent disability (Jorge, 2005). Pre-injury substance abuse places an individual at a greater risk of experiencing a fatal TBI (Foulkes, et al., 1991; Harrison-

Felix, Whiteneck, DeVivo, Hammond, & Jha, 2004), while alcohol intoxication is often associated with longer lasting cognitive and behavioural problems following injury (Bombardier, 1995; Chua, Ng, Yap, & Bok, 2007; Corrigan, 1995; Styrke, Stalnacke, Sojka, & Bjornstig, 2007).

The majority of TBIs are sustained by young people between the ages of 15 and 24 years, with the highest incidence rates for persons under 40 years of age and those aged 75 years or older (Dieli, 2002; Styrke, et al. 2007). Young males have twice the risk of suffering a TBI and their injuries tend to be more severe (Bruns & Hauser, 2003). However, this gender difference is reversed in elderly persons, where females are more likely to experience a TBI (Bruns & Hauser, 2003; Chua, et al. 2007).

Persons who have sustained a TBI are at an increased risk of experiencing further TBIs, regardless of injury severity, and these additional TBIs may have an adverse and cumulative impact on the cognitive and behavioural impairments that an individual experiences (Guskiewicz, et al., 2003; Thornhill, et al., 2000). Indeed, few individuals who experience serious persistent cognitive and behavioural deficits following a TBI resume their premorbid level of functioning or return to prior levels of employment (Wehman, Targett, West, & Kregel, 2005).

Road traffic accidents are the primary cause of TBI in young adults (Brouwer, Withaar, Tant, & Van Zomeren, 2002; Javouhey, et al. 2006), particularly when alcohol is involved (Chua, et al. 2007; Thornton, Vink, Blumbergs, & Van den Heuvel, 2006). Indeed, road crashes account for nearly half of all TBIs (Javouhey, et al. 2006; Lee, Seow, & Ng, 2006) and are the third highest cause of death and disability in the world (Yates & Roberts, 2000). Falls are the main cause of TBI for young children and persons aged 75 years and older, with other causes including assaults, and occupational and recreational injuries (Baguley, et al. 2000; Bruns & Hauser, 2003; Chua, et al. 2007; Jennett, 1996).

1.1.2 Types of TBI

There are two main types of TBI, penetrating and non-penetrating. Penetrating head injuries account for less than 10% of all TBIs (Baguley, et al. 2000) and are characterised by a focal brain lesion that results when the skull and dura of the brain are penetrated by a missile or when there is a severe depressed skull fracture (Schwab, Grafman, Salazar, & Kraft, 1993). A non-penetrating traumatic brain injury arises when brain tissue is bruised and strained as a result of an impact to, and acceleration/deceleration of, the head (Marion, 1999). Non-penetrating injuries account for over 90% of all TBIs (Baguley, et al. 2000) and are, therefore, the focus of the current research.

1.2 Neuropathology of TBI

Contact and inertial forces are the two primary mechanisms implicated in the neuropathology of non-penetrating TBI. Contact forces arise when the head impacts with a solid object and are responsible for focal damage to the brain at the site of impact (coup contusions) and remote from the initial impact site (contrecoup contusions), as well as skull fractures (Bhateja, Shukla, Devi, & Kolluri, 2009). Inertial forces occur when a sudden acceleration of the head, with or without force, causes a differential motion of the brain relative to the skull (Dieli, 2002). Acceleration forces are the main mechanism of injury implicated in concussion, contrecoup contusions (focal damage to the brain remote from the site of impact), diffuse axonal injury (DAI) (tearing or shearing of white matter connecting various brain structures) and diffuse vascular injury (multiple small haemorrhages) (Pittella & Gusmao, 2003; Scheid, Preul, Gruber, Wiggins, & Yves von Cramon, 2003) following a TBI. Both contact and inertial forces lead to primary and secondary brain injury (Granacher, 2008).

Primary injury occurs at the moment of impact and includes a variety of injuries, of which focal cortical contusions (local abrasions of neurons, axons and blood vessels at the brains surface), DAI and diffuse vascular injury are the most common types (Ogata, 2007;

Taber, Warden, & Hurley, 2006). Focal cortical contusions are characteristically located in the frontal and temporal lobes, and have been associated with impairments in cognition, personality, and mood (Babin, 2003). DAI affects long white matter axons and the grey-white brain matter interface (Golden, Moses, Coffman, Miller, & Strider, 1983; Kraus, et al., 2007) and is associated with cognitive deficits, prolonged loss of consciousness and poorer outcome following TBI (Kraus, et al. 2007). In addition, DAI can result from secondary or delayed brain injury (Ashley, 2004; Bramlett & Dietrich, 2002; Novack, Dillon, & Jackson, 1996). Diffuse vascular injury primarily appears in the frontal lobes, temporal lobes, and white matter of the brain (Ogata, 2007) and can raise intracranial pressure and increase the risk of coma following TBI (Scheid, et al. 2003).

Brain damage that results from the primary impact is immediate and irreversible, and can only be reduced by preventative strategies such as educational programs to reduce the incidence of TBI and the use of safety measures to minimise the severity of damage that the brain sustains (e.g., seat belts and helmets) (Binder, Corrigan, & Langlois, 2005; Finfer & Cohen, 2001; Vink & Nimmo, 2009). In contrast, secondary injury mechanisms are delayed following TBI. This provides a brief time frame within which pharmacological agents may be administered to reduce, or limit the impact of, some of the secondary biochemical changes that cause additional brain damage and poorer outcome following injury (Finfer & Cohen, 2001; Katayama, Becker, Tamura, & Hovda, 1990). It is these secondary biochemical events that are the focus of the current research.

There are a variety of secondary biochemical changes in the brain that can give rise to cellular damage following a TBI which can be even more destructive to brain tissue than the primary injury (Cernak, et al., 2004; Muizelaar, 1994; Siesjo & Siesjo, 1996). These changes include a decrease in the supply of oxygen to the brain, as well as alterations to neurotransmitter levels, ion homeostasis and metabolism (Finfer & Cohen, 2001; Kochanek,

Clark, & Jenkins, 2007; Vink & Nimmo, 2009) and provide a potential target for pharmacological treatments. Chapter 2 provides a detailed review of these secondary biochemical changes. The severity of a TBI is related to the location and extent of primary and secondary damage, and the metabolic state of the brain prior to the onset of injury, with more extensive damage associated with a more severe injury and poorer outcome (Corrigan, 1995; Garnett, et al., 2000; Marino, et al., 2007).

1.2.1 Measurement of injury severity following TBI

TBIs are frequently categorised into three severity levels: mild, moderate and severe. While severe injuries are associated with an elevated risk of neuropathological abnormalities and an increased risk of long-term cognitive and behavioural problems (Zasler, Katz, & Zafonte, 2007), a substantial minority of mild TBI patients also experience long-term neuropsychological deficits (Guha, 2004; Sterr, Herron, Hayward, & Montaldi, 2006).

A number of measures are commonly used to assess injury severity following a TBI. One of these measures is the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974), which measures eye opening, motor response and verbal response, in order to assess a patient's level of wakefulness or responsiveness following injury (McKinlay, Brooks, Bond, Martinage, & Marshall, 1981). Scores range between 3 and 15, with a patient classified as having a severe injury if they have a GCS score between 3 and 8, a moderate injury if the score is between 9 and 12, and a mild injury if the GCS score is between 13 and 15 (McKinlay, et al., 1981).

A second measure of injury severity is the duration of post-traumatic amnesia (PTA), which refers to the period of memory loss immediately following an injury (McKinlay, et al., 1981). A PTA of less than 60 minutes, is classified as a mild injury, a PTA lasting up to 24 hours represents a moderate injury, while a PTA longer than one day is classified as a severe injury (McKinlay, et al., 1981). Another common measure of injury severity is duration of loss of consciousness (LOC). A mild injury is associated with a LOC that lasts less than 20

minutes, a moderate injury with a LOC that lasts from 20 minutes to 36 hours, and a severe injury has a LOC lasting over a week (Silver, McAllister, & Yudofsky, 2005).

Each of these indices of injury severity have shown a relationship to subsequent cognitive and behavioural outcome (Dikmen, Machamer, Winn, & Temkin, 1995; Hoofien, Gilboa, Vakil, & Donovick, 2001). However, while the number and nature of cognitive and behavioural deficits that an individual experiences is related to the severity of the injury (Levin & Kraus, 1994; Levin, Williams, Eisenberg, High, & Guinto, 1992), there is still considerable individual variability in outcome and recovery following TBI. For example, more severe and persistent cognitive and behavioural impairments are generally associated with older age groups, certain premorbid factors (e.g., lower education and intelligence, pre-injury personality and emotional problems), and alcohol-related changes to the brains metabolism (Corrigan & Deutschle, 2008; Jorge, 2005; Poon, Zhu, Ng, & Wong, 2005). Each of these factors may also need to be taken into account when considering an individual's outcome following TBI (Bajo & Fleminger, 2002).

1.3 Outcomes following TBI

Changes to cognition, together with alterations to emotional state and personality, are the most frequently reported neuropsychological changes following TBI and tend to have the most far reaching consequences for social, occupational, and educational recovery (Jorge, 2005).

1.3.1 Cognitive changes

Impairments in memory, attention, speed of information processing (Brauer, et al., 2004; Feinstein, 2006), and executive function (Feinstein, 2006; Khan, et al., 2003) are the most commonly found cognitive deficits after TBI. Deficits in learning and *memory* are associated with damage to the frontal and temporal lobes and are one of the most pervasive

symptoms following a TBI (Levin, 1989; Vakil, 2005). These impairments in memory initially involve a loss of memories both immediately prior to and following the traumatic event and, in the later post-injury stages, present as an inability to store new memories (Van Zomeren & Saan, 1990). Problems with working memory, verbal memory (Feinstein, 2006), prospective memory (Fleming, Shum, Strong, & Lightbody, 2005), and long term memory (Thornhill, et al., 2000), as well as an impaired ability to learn new information (Khan, et al., 2003) may persist for a year or more post-injury (Kersel, Marsh, Havill, & Sleigh, 2001). Moreover, deficits in working memory have been found to be predictive of unemployment, poor community integration, and reduced life satisfaction for up to ten years following a TBI and across a range of injury severities (Wood & Rutterford, 2006).

Problems with *attention* are also frequently reported by individuals after a TBI (Brauer, et al., 2004; Feinstein, 2006; Mathias & Wheaton, 2007). While there is some debate within the literature as to whether cognitive deficits following TBI, including attention deficits, represent a specific deficit or result from a more general cognitive slowing (Brouwer, et al., 2002; Mathias & Wheaton, 2007; Rassovsky, et al., 2006b; Rios, Perianez, & Munoz-Cespedes, 2004), impairments in selective, focused, divided and sustained attention have been noted across a range of injury severities (Chan, 2000; Mangels, Craik, Levine, Schwartz, & Stuss, 2002; Rios, et al., 2004). Importantly, a more general deficit in information processing speed has also consistently been found (Brouwer, et al., 2002; Felmingham, Baguley, & Green, 2004; Mathias & Wheaton, 2007; Ponsford & Kinsella, 1992). Deficits in attention may persist for a year or more post-injury (Spikman, Timmerman, vanZomeren, & Deelman, 1999) and can impair occupational, social and emotional adjustment following TBI (Engberg & Teasdale, 2004; Hart, Whyte, Kim, & Vaccaro, 2005).

Impaired *executive function* is typically linked with damage to the pre-frontal lobes and white matter tracts, and may include poor planning and organisation, as well as reduced

cognitive flexibility and judgement, particularly when dealing with new or unfamiliar situations (Bivona, et al., 2008; Fork, et al., 2005; High, Sander, Struchen, & Hart, 2005; Marsh & Sleigh, 2002; McDonald, Flashman, & Saykin, 2002). Various aspects of executive function have shown impairment across a range of injury severities following TBI including, verbal and non-verbal fluency (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Fork, et al., 2005; Mathias, Beall, & Bigler, 2004), mental flexibility (Bivona, et al., 2008; Kim, et al., 2005; Zakzanis, Leach, & Kaplan, 1999), concept formation (Fork, et al., 2005), inhibition and impulse control (Bivona, et al., 2008; Hart, et al., 2005; Kim, et al., 2005), and initiation in goal-directed behaviour (Kim, et al., 2005). Moreover, damage to the pre-frontal lobes can impair an individual's ability to control and organise information, which may additionally impact on memory (Fork, et al., 2005) and complex attention (e.g., dual-task performance) after injury (Bivona, et al., 2008; Fork, et al., 2005; Granacher, 2008; Hart, et al., 2005; Kim, et al., 2005), further complicating cognitive recovery. Deficits in executive function can hinder rehabilitation, return to work, activities of daily living and social reintegration (Bivona, et al., 2008; Kim, et al., 2005), and may persist for over a year after a mild TBI (Vanderploeg, Curtiss, & Belanger, 2005) and for considerably longer following a moderate to severe injury (Kim, et al., 2005).

1.3.2 Behavioural changes

Behavioural changes after TBI include alterations to personality or emotional stability, as well as more general deficits in psychosocial function. *Personality* change is perhaps the most disabling and persistent behavioural problem that people experience following TBI (Van Zomeren & Saan, 1990) and is typically associated with damage to the pre-frontal and anterior temporal regions of the brain. Altered personality has been identified in persons that have sustained a TBI from three months (Brooks & McKinlay, 1983) to as long as 30 years after injury (Hibbard, et al., 2000; Koponen, et al., 2002).

A number of personality changes have been reported following TBI including antisocial, avoidant, and narcissistic behaviour (Gordon, Haddad, Brown, Hibbard, & Sliwinski, 2000; Hibbard, et al., 2000; Koponen, et al., 2002), impaired self-awareness (Bach & David, 2006), and self-monitoring of behaviour, as well as disinhibition (Handel, Ovitt, Spiro, & Rao, 2007) and apathy (Kant, Duffy, & Pivovarnik, 1998), which may lower self-esteem and impact on family life and social reintegration (Khan, et al., 2003; Van Zomeren & Saan, 1990). However, the injury itself is not the sole determinant of altered personality, with premorbid personality and the presence of pre-existing psychiatric disorders, including a history of alcohol and drug abuse (Fann, et al., 2004; Hibbard, et al., 2000; Jorge, 2005), also thought to play a role in post-injury personality changes (Rassovsky, et al., 2006a).

TBIs can also give rise to a variety of *emotional changes* for weeks, months or even years post-trauma, including anxiety, depression and post-traumatic stress disorder (Khan, et al., 2003; Ponsford, Olver, & Curran, 1995; Van Zomeren & Saan, 1990). *Anxiety*, disorders are found in up to 25% of persons that have sustained a TBI (Fann, Katon, Uomoto, & Esselman, 1995). The symptoms of anxiety following TBI include intense and frequent apprehension or fear that is out of proportion to the source of worry, excessive concern with everyday situations (e.g., work, health, family, money), as well as somatic complaints which include headaches, fatigue, blurred vision and difficulty breathing, swallowing and concentrating (Hiott & Labbate, 2002). Anxiety disorders may also be accompanied by depressive symptoms, particularly when the right hemisphere of the brain is damaged (Fann, et al., 1995; Jorge, Robinson, Starkstein, & Arndt, 1993).

Depression is the most prevalent psychiatric disturbance following a TBI with more than 50% of individuals likely to experience a major depressive episode after trauma (Bombardier, et al., 2010). The symptoms of depression may emerge from one to twelve months post-injury (Bombardier, et al., 2010; Levin, et al., 2001) in response to the cognitive,

physical and occupational losses that the injury has caused (Engberg & Teasdale, 2004; Van Zomeren & Saan, 1990). The severity of the injury (Testa, Malec, Moessner, & Brown, 2006), together with any pre-injury psychiatric history (Jorge, 2005) and a growing awareness of injury–related deficits (Godfrey, Partridge, & Knight, 1993), places an individual at an increased risk of experiencing depression, anxiety, and poor psychosocial outcome. While depression can have a negative impact on the number of physical, cognitive, and psychosocial problems that an individual reports after a TBI, treatment can reduce the associated cognitive dysfunction (Feinstein, 2006). Depression can also increase the number of stress-related symptoms that an individual reports (Fann, et al., 1995).

A quarter of all persons that sustain a TBI develop *post-traumatic stress disorder* (Bryant & Harvey, 1998; Bryant, Marosszeky, Crooks, Baguley, & Gurka, 2000) as a result of psychological stressors associated with the traumatic event and the head injury itself (Glaesser, Neuner, Lutgehetmann, Schmidt, & Elbert, 2004). Persons that develop post-traumatic stress disorder can experience elevated arousal and panic when they are confronted with a situation similar to the one in which the injury occurred (Bryant, 2001; Gouick & Gentleman, 2004). In addition, recurring experiences of the traumatic event (e.g., intrusive memories or nightmares), may give rise to psychological and physiological distress, withdrawal and emotional lability (Bryant, 2001; Glaesser, et al., 2004; Saunders, McDonald, & Richardson, 2006), particularly in those individuals that remain conscious after an injury (Glaesser, et al., 2004). Moreover, the increased anxiety that results from the cognitive and physical limitations produced by the injury, together with disinhibition, may also provoke aggressive behaviour, which is frequently reported in patients who have sustained a TBI (Bryant, 2001; Deb, Lyons, & Koutzoukis, 1998; Van Zomeren & Saan, 1990).

The abovementioned cognitive and behavioural problems can also have a negative impact on *psychosocial function* (quality of life, functional recovery, occupational, personal

and social engagement) (Engberg & Teasdale, 2004), with more severe injuries associated with greater disability and poorer vocational and social reintegration (Engberg & Teasdale, 2004; Oddy, Coughlan, Tyerman, & Jenkins, 1985; Van Zomeren & Saan, 1990). Social withdrawal and isolation is particularly common after TBI as patients are faced with altered cognition and personality. Indeed the restlessness, irritability, aggression, and childish behaviour often exhibited by individuals following injury may cause patients to lose contact with work associates and friends as they become increasingly unable or unwilling to re-enter occupational or social situations (Engberg & Teasdale, 2004; Khan, et al., 2003). Moreover, alterations in personality and emotion can place considerable stress on marital situations, with divorce rates particularly high in relationships where one member of the couple has sustained a TBI (Khan, et al., 2003; Van Zomeren & Saan, 1990).

While emotional state and the ability to maintain interpersonal relationships at a pre-injury level are important predictors of survival following a TBI (Rassovsky, et al., 2006a; Satz, Forney, et al., 1998), cognitive status has been found to be a more important predictor of functional outcome and adaptability (Dawson, Levine, Schwartz, & Stuss, 2004; Rassovsky, et al., 2006b). This suggests that treatment strategies aimed at reducing both cognitive and behavioural problems after TBI are vital to improving patient outcome and social reintegration.

1.4 Interventions

In the last thirty years, the fatality rates following TBI have decreased by between 20% (Atabaki, 2006) and 50% (Zink, 2001) which may, in part, be explained by improved road traffic initiatives, (e.g., compulsory seat belt use, speed limit reductions) (Hillary, et al., 2002; Iribhogbe & Osime, 2007; Khan, et al., 2003; Richter, Berman, Friedman, & Ben-David, 2006; Trinca & Dooley, 1977) and the improved medical management of patients following injury (Ghajar, 2000; Peterson, Carson, & Carney, 2008; Rudehill, et al., 2002;

Timofeev, et al., 2006). This has lead to a significant increase in the number of patients who survive their injury but experience long-term and disabling neuropsychological impairments, emphasising the need to discover effective treatment strategies (Eker, et al., 2000). There is a growing interest in the use of pharmacological therapies to attenuate the effects of brain damage caused by a TBI in order to minimise the individual's level of disability. At present, however, post-injury education and rehabilitation are the primary intervention strategies that are used following TBI, with pharmacological interventions often used as an adjunct to reduce cognitive and behavioural impairments that may limit rehabilitation efficacy (Marion, 1999).

1.4.1 Rehabilitation strategies

Rehabilitation aims to maximise an individual's return to normal function. Traumatic brain injury, however, is a heterogeneous injury, not only in terms of the degree of damage that the brain may sustain and the disabilities this will produce but also in terms of an individual's premorbid abilities and predispositions (Jorge, 2005; Parker, 1996; Testa, et al., 2006). Consequently, effective rehabilitation must be tailored to meet the needs of an individual and his or her family (Khan, et al., 2003; Laatsch, Jobe, Sychra, Lin, & Blend, 1997).

Rehabilitation programmes that are designed to improve cerebral functioning by promoting neural plasticity (Kleim & Jones, 2008; Raymont & Grafman, 2006) and teaching compensatory strategies have shown significant long-term improvements in cognition and behaviour for individuals that have sustained a severe TBI (Laatsch, et al., 1997). Moreover, individuals with a severe injury are thought to be capable of recovery for months to years' post-injury, even when rehabilitation is delayed for more than two years after an injury (Ashley, Persel, Clark, & Krych, 1997; Gray, 2000; Wood, McCrea, Wood, & Merriman, 1999). Following mild TBI, educational interventions that reassure individuals by providing information about the symptoms that they are likely to experience appear to be more

beneficial to recovery than intensive rehabilitation programs (Comper, et al., 2005; Paniak, Toller-Lobe, Reynolds, Melnyk, & Nagy, 2000).

1.4.2 Pharmacological treatments

Pharmacological treatments that are given soon after a TBI are designed to play a neuroprotective role by blocking secondary injury processes and minimising damage to the brain in order to improve outcome (Cawley, Marburger, & Earl, 1998; Tolias & Bullock, 2004). In contrast, pharmacological treatments that are administered in the later stages of injury have been used to treat the neuropsychological sequelae of TBI by minimising persistent declines in the availability of biochemicals in the brain that are associated with cognitive and behavioural problems. Treatments that are administered in both the early and post-acute stage of an injury are the focus of this thesis. In order to establish a context for research in this area, it is necessary to understand some of the main biochemical processes that these pharmacological treatments target. These will be discussed in Chapter 2.

Chapter 2: The Pathology of Secondary Injury

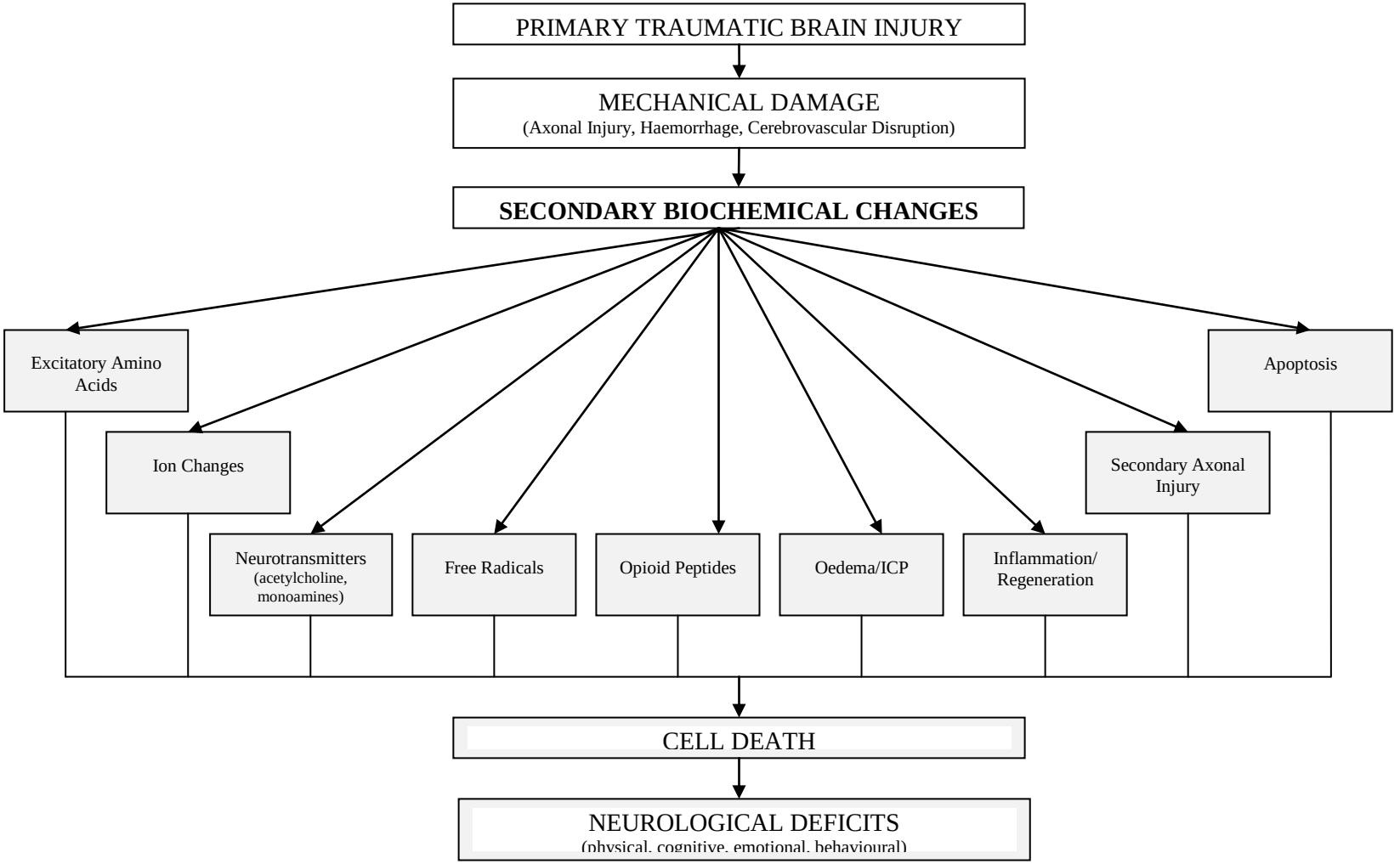
Irreversible damage to brain tissue after a TBI results from both primary and secondary injury. Some of the secondary biochemical changes that take place in the brain following a TBI will now be discussed. However, it is important to note that there is a complex interaction between these biochemical events which, either alone or in combination, lead to neuronal death, axonal degeneration and transient or permanent changes to the structure and function of brain cells (Novack, et al., 1996) in the minutes to days following an injury (Bigler, 2001; Bouma, et al., 1992; Hughes, et al., 2004; Marino, et al., 2007; McQuire, Sutcliffe, & Coats, 1998).

Ischemia (a reduction in blood flow and oxygen supply to the brain) and hypoxia (a deficiency in oxygen supply to the brain) are thought to be initiators of many of the biochemical alterations that take place, resulting in neurotransmitter changes, free radical production, oedema, the triggering of inflammatory and immune response systems, and the initiation of regenerative processes (Hlatky, Valadka, Goodman, Contant, & Robertson, 2004; Hutchinson, 2005; Sarrafzadeh, Kiening, Callsen, & Unterberg, 2003; Sarrafzadeh, Sakowitz, Callsen, Lanksch, & Unterberg, 2000). Specifically, ischemia and hypoxia hinder the production of adenosine triphosphate (Granacher, 2008), which is the major energy source that supports vital cellular processes, including glucose oxidation (via oxidative phosphorylation), and the maintenance of mitochondrial membrane integrity and ion pumping mechanisms (Novack, et al., 1996; Verweij, et al., 2000). The depletion of adenosine triphosphate, and a consequent reduction in the energy supply to the brain leads to marked elevations in extracellular levels of *excitatory amino acids*, including glutamate and aspartate, which are toxic to brain cells and glia when released in high concentrations (excitotoxicity) (Werner & Engelhard, 2007). Energy-dependent *ion* pumps that serve to maintain normal

cellular ion gradients also fail, resulting in unregulated fluctuations in brain levels of calcium, sodium and potassium (Zasler, et al., 2007), the depolarisation of neurons (Novack, et al., 1996) and the over-production of oxygen *free radicals*, leading to lipid peroxidation (chemical destruction of the cell membrane) (Ansari, Roberts, & Scheff, 2008a, 2008b; Clausen, Marklund, Lewen, & Hillered, 2008).

These events facilitate, and are concomitant with, a cascade of additional biochemical and physiological changes that result in delayed cell death and poorer outcome after a TBI. More specifically, there are alterations to *neurotransmitter* production, synthesis and release and a break-down in the blood-brain barrier resulting in *oedema* (an increase in brain water content); as well as *inflammation*, *secondary axonal injury* and *apoptosis* (Zasler, et al., 2007). These secondary biochemical changes are summarised in Figure 1.

Figure 1: Summary of the secondary biochemical changes that occur following TBI



2.1 Secondary biochemical changes

The following discussion will outline the main changes, namely: changes to excitatory amino acids, ion homeostasis, neurotransmitters, free radicals and opioids, as well as the initiation of oedema, inflammation, secondary axonal injury and apoptosis (refer to Figure 1). It will also examine some of the pharmacological agents that have been used to treat them.

2.1.1 Excitatory Amino Acids

Excitatory amino acids such as glutamate and aspartate are normally occurring neurotransmitters in the brain that are essential for normal cell functioning (Baker, Moulton, MacMillan, & Shedden, 1993; Novack, et al., 1996). The excessive release of excitatory amino acids following TBI, and the over-stimulation of glutamate receptors (N-methyl-D-aspartate [NMDA], a-amino-3-hydrocy-5-methyl-4-isoxazolepropionic acid [AMPA], kainite, and metabotropic [mGluR]) (Furukawa, et al., 2003; Novack, et al., 1996), have been associated with neuronal death (Choi, Maulucci-Gedde, & Kriegstein, 1987; McIntosh, Juhler, Raghupathi, Saatman, & Smith, 1999). Abnormally high levels of excitatory amino acids have been found in the brains of rodents for up to thirty minutes after TBI (Bai, Wong, Li, & Fei, 2004; Faden, Demediuk, Panter, & Vink, 1989; Ikonomidou & Turski, 2002) and in the extracellular and cerebrospinal fluid of humans for several days after injury (Baker, et al., 1993; Bullock, et al., 1998). Moreover, high levels are associated with poorer outcome in both groups (Bullock, et al., 1998; Faden, et al., 1989), suggesting that excitatory amino acids play an important role in secondary neural tissue damage and subsequent outcome following TBI.

A range of pharmacological agents that target the excessive release of excitatory amino acids have been examined in both experimental and clinical research. These compounds, including the excitatory amino acid antagonists, act to reduce excitatory neurotransmissions in the brain, either by preventing their release or by blocking excitatory

amino acid receptors, thereby reducing cellular damage and improving outcome (Novack, et al., 1996). Treatment with the NMDA antagonists dextrorphan and 3-(2-carboxypiperazine-4-yl) propyl-1-phosphoric acid, has improved outcome in rodents following TBI (Faden, et al., 1989), while inhibiting glutamate release using the non-competitive NMDA antagonist magnesium sulphate, and the AMPA antagonist YM872, has been shown to reduce tissue loss (Browne, Leoni, Iwata, Chen, & Smith, 2004; Furukawa, et al., 2003). However, these treatment benefits have not translated to human research (Royo, Shimizu, Schouten, Stover, & McIntosh, 2003). For example, clinical trials using phencyclidine, dicocilpine (MK-801) (Novack, et al., 1996), magnesium sulphate (Temkin, et al., 2007) and the NMDA antagonist selfotel (Morris, et al., 1999) all elicited significant adverse side effects in humans.

2.1.2 Ion Changes

A depleted energy supply to the brain after TBI causes energy-dependent ion pumping mechanisms to fail, resulting in profound increases in intracellular levels of calcium, sodium, and extracellular potassium (McIntosh, et al., 1999; Novack, et al., 1996; Silver, et al., 2005; Stiefel, Tomita, & Marmarou, 2005), as well as a marked decline in magnesium (Bareyre, et al., 1999). Increased intracellular levels of calcium trigger a number of other biochemical changes, such as the continued release of excitatory amino acids, cellular depolarisation and excitotoxicity, the uncontrolled activation of toxic enzymes (e.g., phospholipases, proteases, nitric oxide synthases), mitochondrial dysregulation, and the generation of oxygen free radicals (Granacher, 2008; Marion, 1999; McIntosh, et al., 1999).

Persistent and marked increases in intracellular calcium have been observed in rodents (Fineman, Hovda, & Smith, 1993) and cats (Hubschmann & Nathanson, 1985) following TBI, and are associated with tissue damage at the site of the contusion (Fineman, et al., 1993), an increase in brain water content (Shapira, Yadid, Cotev, & Shohami, 1989) and cellular membrane destabilisation (Hubschmann & Nathanson, 1985). A link has also been observed

between increased extracellular potassium concentrations after TBI and widespread depolarisation (Golding, Steenberg, Johnson, & Bryan, 2000), astrocytic swelling, impaired glucose metabolism, altered energy homeostasis (Katayama, et al., 1990; McIntosh, et al., 1999) and vasoconstriction (Golding, et al., 2000). Moreover, elevated levels of sodium following experimental TBI have been associated with a prolonged period of oedema (Soares, Thomas, Cloherty, & McIntosh, 1992).

Decreased brain levels of free magnesium have also been found in rodents (Heath & Vink, 2001; Suzuki, et al., 1997; Vink, Donkin, Cruz, Nimmo, & Cernak, 2004) and humans (Cernak, et al., 2000; Stippler, et al., 2007) after TBI. Magnesium is thought to play an important role in a number of cellular processes, including the regulation of calcium, sodium and potassium ions which if disturbed may contribute to the development of oedema, enzymatic reactions that sustain cellular energy levels, protein synthesis, oxidative stress and, the maintenance of mitochondrial membrane integrity (Bareyre, et al., 1999; McIntosh, et al., 1999; Suzuki, et al., 1997).

With respect to pharmacological treatments aimed at minimising these ion changes, calcium channel blockers (e.g., ziconitide, SNX-185, nimodipine) have shown neuroprotective effects in animal models of TBI (Berman, Verweij, & Muizelaar, 2000; Lee, Galo, Lyeth, Muizelaar, & Berman, 2004; Royo, et al., 2003), ischemia (Lemons, Chehrazi, Kauten, Hein, & Wagner, 1993), and intracerebral haemorrhage (Ma & Zhang, 2006) but, following human TBI, the results have been mixed. For example, administering nimodipine to persons soon after a severe TBI (6 – 24 hours post-injury), resulted in a favourable but non-significant improvement in outcome, as measured by the Glasgow Outcome Scale (GOS) at six months post-injury (Bailey, et al., 1991; Pillai, Kolluri, Mohanty, & Chandramouli, 2003). Though the drug appeared to be well tolerated, it was concluded that nimodipine was unlikely to have had a marked impact on outcome (Bailey, et al., 1991; Pillai, et al., 2003). Research

has also shown that potassium channel blockers (Mauler, et al., 2004) and sodium channel blockers (Okiyama, et al., 1995) reduce oedema formation and intracranial pressure following subdural haematoma and TBI in rats, while the sodium channel blocker carbemazepine helps to reduce combative behaviour in humans (Azouvi, et al., 1999).

2.1.3 Neurotransmitters (acetylcholine, monoamines)

TBI can alter a number of neurotransmitter systems in the brain that have been implicated in cognitive and behavioural problems following injury. Disruptions to *acetylcholine* has been identified in both rodents (Gorman, Fu, Hovda, Murray, & Traystman, 1996; Verbois, Scheff, & Pauly, 2002) and humans (Dewar & Graham, 1996; Murdoch, Nicoll, Graham, & Dewar, 2002) following injury, and these changes have been linked to disturbances in memory and attention (Arciniegas, et al., 1999; Tenovuo, 2006). Functionally, acetylcholine acts on both the nicotinic and muscarinic receptors in the brain (Webster, 2003), which are primarily distributed in the forebrain and brainstem, with cognitive disturbances linked to a disruption in the cholinergic activity of the hippocampus.

Experimental research suggests that changes to cholinergic receptor sensitivity as well as decreased concentrations of acetylcholine in the brain may be responsible for the cognitive problems that result from a TBI (Lyeth, Jiang, Delahunty, Phillips, & Hamm, 1994). For example, rodent research has shown that an early increase in acetylcholine concentration after injury, is followed by a decrease in muscarinic and nicotinic cholinergic receptor binding (Gorman, et al., 1996; Sihver, et al., 2001; Verbois, et al., 2002), as well as a decrease in the enzyme that mediates the biosynthesis of acetylcholine (choline acetyl transferase [ChAT]) (Wenk, Sweeney, Hughey, Carson, & Olton, 1986). However, post-mortem examinations of human brains have found that there were no alterations to the binding of either muscarinic or nicotinic cholinergic receptors after injury (Dewar & Graham, 1996; Murdoch, Perry, Court, Graham, & Dewar, 1998), suggesting that a depletion in acetylcholine, rather than decreased

receptor binding may be responsible for the memory problems that are often found following human TBI (Hatton, 2001; Oda, 1999).

Pharmacological treatments that target the profound changes in cholinergic function that typically accompany TBI have shown some efficacy in reducing cognitive deficits following injury. Specifically, rodents treated with the acetylcholinesterase inhibitor, rivastigmine, soon after injury showed improved neurologic and functional outcome (Chen, Shohami, Bass, & Weinstock, 1998; Chen, Shohami, Constantini, & Weinstock, 1998), while early treatment with citicholine (an intermediate in the biosynthesis of acetylcholine) improved memory and reduced post-concussion symptoms in humans (Levin, 1991). With respect to persistent disruptions to acetylcholine, a number of acetylcholinesterase inhibitors (e.g., donepezil, physostigmine, galantamine) have shown efficacy in reducing cognitive deficits in a human TBI population. For example, improvements in memory, attention, executive function and learning (Khateb, Ammann, Annoni, & Diserens, 2005; Taverni, Seliger, & Lightman, 1998), as well as full scale IQ (intelligence quotient) (Whelan, Walker, & Schultz, 2000) have been reported following treatment with donepezil, with more substantial improvements being associated with early administration (Walker, et al., 2004). Treatment with either donepezil or galantamine improved memory and general cognitive function, however, this was attributed to an improvement in attention (Tenuvuo, 2005), rather than improvements to specific cognitive functions. In contrast, persons with severe TBI that were treated with physostigmine (plus L-dopa) showed increased motor activity but did not always show clinical improvement (van Woerkom, Minderhoud, & Nicolai, 1982).

Monoamines refer to a chemical group of neurotransmitters including serotonin, dopamine, and norepinephrine (Webster, 2003) and are typically disrupted following TBI. Elevated concentrations of *serotonin* have been identified in both rodents (Busto, Dietrich, Globus, Alonso, & Ginsberg, 1997) and humans after injury (Markianos, Seretis, Kotsou,

Baltas, & Sacharogiannis, 1992), and this been associated with poorer outcome (Markianos, et al., 1992). Experimental research has also found a significant increase in hypothalamic concentrations of dopamine and norepinephrine in rats within one hour of a TBI (Kobori, Clifton, & Dash, 2006; McIntosh, Yu, & Gennarelli, 1994; Prasad, et al., 1994; Xu, Zhou, Jiang, Wang, & Chen, 2005), as well as marked and persistent decreases in dopamine and norepinephrine concentrations in the injury cortex (McIntosh, et al., 1994; Prasad, et al., 1994). Increased dopamine and norepinephrine activity have also been observed in humans (Markianos, Seretis, Kotsou, & Christopoulos, 1996), while long-term alterations to dopaminergic pathways and neuronal functioning have been linked to transient and persistent cognitive deficits (Bales, Wagner, Kline, & Dixon, 2009; Schneider, Drew-Cates, Wong, & Dombovy, 1999).

Treatments that minimise early declines in serotonin and dopamine have shown efficacy in experimental models of TBI. For example, serotonergic (e.g., 8-OH-DPAT) (Kline, Yu, Massucci, Zafonte, & Dixon, 2002) and dopaminergic agents (e.g., haloperidol, methylphenidate) (Kline, Yan, Bao, Marion, & Dixon, 2000; Tang, Noda, & Nabeshima, 1997) have improved neurological and functional outcome in rodents. In addition, when administered soon after injury, the dopamine agonist, amantadine, and the serotonin agonist, repinotan have improved outcome (arousal and global outcome) in humans (Ohman, Braakman, & Legout, 2001; Saniova, Drobny, Kneslova, & Minarik, 2004).

In terms of long-term disruptions to these neurotransmitters, clinical research has shown that serotonergic (amitriptyline, sertraline), and dopaminergic (amantadine, methylphenidate) treatments (Chandler, Barnhill, & Gualtieri, 1988; Fann, Uomoto, & Katon, 2000; Gualtieri & Evans, 1988; Masanic, Bayley, vanReekum, & Simard, 2001; Mysiw, Jackson, & Corrigan, 1988) improve cognition (attention, speed of information processing) and behaviour (agitation, anxiety, depression) in humans, although in some cases the findings

have been mixed (Horsfield, et al., 2002; Karli, et al., 1999; Kraus, et al., 2005; Lee, et al., 2005; McDowell, Whyte, & D'Esposito, 1998; Nickels, Schneider, Dombovy, & Wong, 1994). For example, a case study examining treatment with amantadine showed that, while there were initial improvements in mood and initiation, this was followed by a worsening in agitation and hallucinations (McDowell, et al., 1998).

2.1.4 Free Radicals

An increase in glutamate production and a subsequent rise in intracellular calcium ions following TBI, results in the breakdown of cell membrane phospholipids and the formation of free fatty acids leading to the excessive generation of highly reactive oxygen species and free radicals (Clausen, et al., 2008; Globus, Alonso, Dietrich, Busto, & Ginsberg, 1995; Hall, Vaishnav, & Mustafa, 2010; Lewen & Hillered, 1998). The over-production of oxygen free radicals can cause oxidative stress (an imbalance between oxidants and anti-oxidants in the brain) and lipid peroxidation (chemical damage to the cell membrane), as well as protein oxidation (oxidative modification of proteins), damage to nucleic acids and mitochondria, deoxyribonucleic acid (DNA) fragmentation, alterations to signal transduction (converting a chemical stimulus to a cellular response), and disruption to the blood-brain barrier (Ansari, et al., 2008a; Clausen, et al., 2008; Dhar, et al., 1996; Lelli, Becks, Dabrowska, & Hinshaw, 1998; Smith, Andrus, Zhang, & Hall, 1994).

Although, under normal circumstances, naturally occurring antioxidants protect the brain from oxidative damage, research in rodents has shown that decreased levels of antioxidants coupled with an increase in oxidants may result in irreversible damage to brain tissue (Ansari, et al., 2008a; Dhar, et al., 1996; Globus, et al., 1995; Toklu, et al., 2009). This has been supported in human research, where a marked increase in oxygen free radicals has resulted in oxidative stress and cellular damage within forty-eight hours of a severe TBI (Dhar, et al., 1996). Moreover, the administration of antoxidants (e.g., alpha lipoic acid,

NXY-059, PBN, S-PBN, U-74006F) significantly attenuated the increased production of reactive oxygen species (Marklund, Clausen, Lewen, et al., 2001; Marklund, Clausen, McIntosh, & Hillered, 2001), reduced blood-brain barrier permeability (Smith, et al., 1994; Toklu, et al., 2009), tissue loss (Clausen, et al., 2008) and oedema (Toklu, et al., 2009) in rodents following TBI. In addition, clinical research has shown that the oxygen radical scavenger pegorgotein (PEG-SOD) minimised the duration of elevated intracranial pressure and improved outcome (GOS) at three, but not six months, after a severe TBI (Muizelaar, et al., 1993).

2.1.5 Opioid Peptides

Opioid peptides are thought to play a vital role in a number of cellular and systemic processes following TBI (Grigoriants, Pravdenkova, Andersen, & Desiderio, 1995; Heath & Vink, 1999b) via their actions at the kappa (κ), mu (μ) and delta (δ) receptors (Qi & Smith, 2006). Marked increases in brain concentrations of opioid peptides have been observed in rodents (Grigoriants, et al., 1995), cats (McIntosh, Head, & Faden, 1987) and newborn pigs (Armstead, 1995; Armstead & Kurth, 1994) after injury, and this has been associated with damage to neural tissue (McIntosh, et al., 1987), alterations to vascular activity (vasodilation, vasoconstriction) (Armstead, 1995; Armstead & Kurth, 1994), and motor deficits (Faden, 1992). In addition, elevated levels of opioid peptides (β-endorphin, leu-enkephalin, met-enkephalin) found in the cerebrospinal fluid of humans twenty-four hours or more after a TBI (Pasaoglu, Karakucuk, Kurtsoy, & Pasaoglu, 1996; Stachura, Kowalski, Obochowicz, Huzarska, & Herman, 1997) have been associated with higher mortality following a severe injury (Stachura, et al., 1997) but not poorer arousal (Glasgow Coma Scale) in individuals with TBIs of varying severity (Pasaoglu, et al., 1996).

In addition to their activity at opioid receptor sites, opioid peptides are thought to exert non-opioid effects on secondary injury processes via their actions at NMDA receptors

(Schwarzer, 2009). For example, rodents that were administered the κ-opioid peptide dynorphin, showed a marked increase in the excitatory neurotransmitters glutamate and aspartate (Faden, 1992), while treatment with the non-specific opioid receptor antagonist nalmefene minimised glutamate release following ischemia (Graham, Shimizu, Newman, Weinstein, & Faden, 1993) and reduced motor deficits after spinal cord injury (Bakshi, Newman, & Faden, 1990). Moreover, the NMDA antagonist ketamine, which also binds weakly to opioid receptors, reduced depolarization in humans after severe TBI and intracranial hemorrhage (Sakowitz, et al., 2009). These findings indicate that alterations in opioid concentrations are closely linked to excitotoxic injury processes (Caudle & Isaac, 1988; Graham, et al., 1993) and suggests that excitotoxicity plays an important role in the secondary pathology of TBI (Faden, 1992).

2.1.6 Oedema/ICP (Vasogenic, Cytotoxic)

Oedema is a major contributor to cellular damage, raised intracranial pressure (ICP), and mortality after TBI (Feickert, Drommer, & Heyer, 1999; Marmarou, et al., 2000; Vink & Nimmo, 2002). Cytotoxic and vasogenic oedema are the two main forms of brain oedema (Barzo, Marmarou, Fatouros, Corwin, & Dunbar, 1996; Barzo, Marmarou, Fatouros, Hayasaki, & Corwin, 1997). Cytotoxic oedema leads to increased intracellular water content and swelling as a result of disruptions to cellular metabolism and ion gradients (Donkin & Vink, 2010; Liang, Bhatta, Gerzanich, & Simard, 2007; Reulen, 1976). Vasogenic oedema, on the other hand, is typified by endothelial damage (injury to the cerebrovascular lining) and blood-brain barrier disruption (Donkin & Vink, 2010), leading to increased brain water content, brain swelling and elevated intracranial pressure.

Evidence of both cytotoxic and vasogenic oedema have been observed in the rat brain from four to twenty-four hours after a TBI (Baskaya, Rao, Dogna, Donaldson, & Dempsey, 1997; Van Putten, Bouwhuis, Muizelaar, Lyeth, & Berman, 2005) and in the human brain for

up to eighteen days after injury (Baskaya, et al., 1997; Liu, Maldjian, Bagley, Sinson, & Grossman, 1999). Although the time course for the development of each type of oedema varies, it is generally considered that vasogenic oedema occurs soon after TBI, whereas cytotoxic oedema is delayed (Schneider, et al., 2002).

The view that vasogenic oedema is the primary source of brain swelling and increased intracranial pressure following TBI (Reulen, 1976) results from the fact that cytotoxic cellular swelling cannot be directly linked to an increase in brain water content (Liang, et al., 2007). However, while experimental research has shown that there is a delayed increase in blood-brain barrier permeability following injury, signifying a secondary period of vasogenic oedema, this breach alone does not lead to an increase in brain fluid (Baskaya, et al., 1997). In addition, brain imaging has shown that there is an immediate and delayed increase in brain fluid following experimental TBI (Barzo, et al., 1997), suggesting that both vasogenic and cytotoxic oedema mediate increased brain water content and intracranial pressure (Barzo, et al., 1997). It has, therefore, been hypothesised that the delayed formation of oedema after TBI may result from the combined effects of a secondary breach of the blood-brain barrier (Baskaya, et al., 1997) and the leakage of ions and water from the vasculature as a result of cytotoxic cell death and dysfunction (Donkin & Vink, 2010; Liang, et al., 2007).

A number of treatments have been found to reduce oedema after TBI. For example, the inhibitor of glutamate release and AMPA receptor antagonist, YM827 (Furukawa, et al., 2003), the phospholipid intermediate and inhibitor of free radical production, citicholine (Baskaya, Dogan, Rao, & Dempsey, 2000), the novel nitric oxide synthase inhibitor, 4-amino-tetrahydro-L-biopterine (Terpolilli, et al., 2009), and the highly specific bradykinin B_2 receptor antagonist, LF 16-0687 Ms (Kaplanski, et al., 2002) have all reduced oedema and improved outcome in rodents. The bradykinin B_2 antagonist CP-0127 has also decreased intracranial pressure and improved early arousal (Narotam et al., 1998) and long-term

outcome (GOS) (Marmarou, et al., 1999) in humans following TBI, while the cannabinoid and NMDA antagonist dexanabinol prevented a rise in intracranial pressure (Knoller, et al., 2002) but failed to improve outcome (GOS) at six months (Maas, et al., 2006).

2.1.7 Inflammation/Regeneration

Inflammation is a systemic immune response to neuronal damage that can either increase or reduce the degree of cellular injury that the brain sustains after TBI (Donkin & Vink, 2010; Liang, et al., 2007). Under inflammatory conditions neutrophils and monocytes/macrophages are able to pass through the blood-brain barrier, activating microglia, neurons and astrocytic cells, and triggering the secretion of both pro- and anti-inflammatory cytokines including, tumor necrosis factor, peptides from the interleukin family, intercellular adhesion molecules (e.g., ICAM-1) and nerve growth factors (Cederberg & Siesjo, 2010; Whitney, Eidem, Peng, Huang, & Zheng, 2009).

Increases in pro-inflammatory cytokines (IL-6, IL-1, IL-8, ICAM-1, TNF-*a*, P-selectin, E-selectin, L-selectin, VCAM-1) have been found in rodent brains (Cederberg & Siesjo, 2010; Koedel, et al., 2007; Lenzlinger, et al., 2001; Morganti-Kossmann, Rancan, Otto, Stahel, & Kossmann, 2001) and in the cerebrospinal fluid of humans following TBI (Chen, Hsu, Huang, & Wang, 2008; Lloyd, Somera-Molina, Van Eldik, Waterson, & Wainwright, 2008; Taupin, Toulmond, Serrano, Benavides, & Zavala, 1993; Woodroofe, et al., 1991). These pro-inflammatory molecules are believed to play an important role in secondary damage after injury by contributing to tissue injury, vascular permeability, blood-brain barrier disruption and oedema (Frugier, Morganti-Kossmann, O'Reilly, & McLean, 2010; Kossmann, Hans, Imhof, Trentz, & Morganti-Kossmann, 1996; Morganti-Kossman, et al., 1997; Nimmo, et al., 2004; Whalen, et al., 1998).

In contrast, inflammatory mediators (e.g., microglia and cytokines) can also play a neuroprotective role in the brain after injury (Merrill & Benveniste, 1996). In particular,

microglia may facilitate tissue repair and the production of nerve growth factors that promote neural protection. Microglia and cytokines are also thought to generate a number of growth factors (TGF-β1, TNF-α, NGF, BDNF) that promote neural survival and functional recovery (Kreutzberg, 1996). In addition, elevated concentrations of anti-inflammatory mediators (e.g cytokines IL-10, Transforming Growth Factor-*B*) have been identified in the cerebrospinal fluid of humans following TBI (Donnelly & Popovich, 2008; Kiefer, Lindholm, & Kreutzberg, 1993; Morganti-Kossman, et al., 1997; Oshima, et al., 2009), suggesting their possible neuroprotective role in mediating the inflammatory response to injury.

Treatment with anti-inflammatory agents, including the pro-inflammatory cytokine inhibitors, IL-10 (Knoblach & Faden, 1998), IL-18BP (Yatsiv, et al., 2002), simvastatin, atorvastatin (Wang, et al., 2007) and Minozac (Lloyd, et al., 2008) has reduced inflammation in rodents following TBI, while hypertonic saline-dextran inhibited the inflammatory response in humans (Rhind, et al., 2010). In addition, atorvastatin and simvastatin, (Lu, Goussev, et al., 2004; Lu, Mahmood, et al., 2004; Lu, et al., 2007), as well as the antioxidant, minocycline (Bye, et al., 2007), the vitamin, nicotinamide (Hoane, Tan, Pierce, Anderson, & Smith, 2006), and the C1 esterease inhibitor, C1-INH (Longhi, et al., 2009), have been linked to increased neuronal survival and improved outcome in experimental models of TBI.

Steroids (e.g., methylprednisolone, triamcinolone, dexamethasone) have also been shown to reduce intracranial pressure and improve outcome following human TBI (Giannotta, Weiss, Apuzzo, & Martin, 1984; Grumme, et al., 1995; Hoppe, Christensen, & Christensen, 1981), although the findings have been mixed. For example, methylprednisolone is a glucocorticoid (hormone important to brain metabolism) that appears to exhibit anti-inflammatory effects by preventing lipid peroxidation caused by the excessive production of free radicals and by reversing calcium accumulation in cells (Novack, et al., 1996). Moreover, when given in high doses within six hours of injury, this treatment has been

associated with increased survival, although no differences in long-term outcome based on the GOS have been found (Giannotta, et al., 1984; Saul, Ducker, Salcman, & Carro, 1981). In contrast, a large-scale randomised controlled trial found that methylprednisolone administered within eight hours of injury may lead to *greater* mortality and *worse* outcome (CRASH Trial Collaborators, 2005).

2.1.8 Secondary Axonal Injury

Axonal damage can result from either immediate impact forces which tear and shear axons following TBI, or as part of a delayed secondary injury process that occurs when axonal transport is impaired, leading to reactive axonal swelling and subsequent detachment (Csuka, et al., 1999; Morganti-Kossmann, et al., 1999). Secondary axonal swelling and dysfunction has been found in animals for up to four days (Kochanek, et al., 2007; Stone, Singleton, & Povlishock, 2001) and, in a clinical population, for as long as six months after injury (MacDonald, Dikranian, Bayly, Holtzman, & Brody, 2007; MacDonald, Dikranian, Song, et al., 2007; Yaghmai, Povlishock, & Povlishock, 1992). Moreover, these changes have been linked to poorer outcome and increased mortality (Bendlin, et al., 2008; Ding, et al., 2008; Kraus, et al., 2007; Marino, et al., 2007).

With respect to the treatment of secondary axonal injury, the immunosuppressant, cyclosporine A (Graham, Lawrence, Adams, Doyle, & McLellan, 1988; Kraus, et al., 2007; Stone, et al., 2001), the nucleoside, inosine (Smith, et al., 2007), and the steroid hormone, progesterone (O'Connor, Cernak, Johnson, & Vink, 2007) have all reduced secondary axonal damage in experimental models of TBI. In addition, treatment with the pro- and anti-inflammatory cytokine, TNF-a (Oshima, et al., 2009) resulted in axonal sprouting and improved motor function, suggesting that secondary axonal damage may be amenable to delayed pharmacological interventions.

2.1.9 Apoptosis

The two main mechanisms of neuronal death following TBI are necrosis and apoptosis. Necrosis refers to immediate cell death that results from the initial impact, whereas apoptosis refers to programmed cell death that is delayed and progressive, thereby providing an additional target for pharmacological interventions (Williams, et al., 2001; Zhang, Chen, Jenkins, Kochanek, & Clark, 2005). Apoptosis is characterised by cell shrinkage, DNA fragmentation and cell membrane breakdown (Zhang, Raghupathi, Saatman, LaPlaca, & McIntosh, 1999) that appears to evolve over time in distinct brain regions (Conti, Raghupathi, Trojanowski, & McIntosh, 1998). For example, apoptosis develops in the white matter of the rodent brain from twelve hours after injury, in the hippocampus at forty-eight hours, and in the thalamus at two weeks after injury (Conti, et al., 1998). DNA fragmentation and apoptotic cells (neurons, oligodedroglia, macrophages) have also been identified in the grey and white matter of human brains from five hours to ten days after TBI (Smith, et al., 2000), while both animals and humans show signs of apoptotic cell death for as long as one year after injury (Smith, et al., 1997; Williams, et al., 2001).

Apoptosis is a normal processes of cell death that is designed to eliminate surplus cells during embryonic development and remove aging cells in the adult brain (Clark, Kochanek, Adelson, et al., 2000; Zhang, et al., 2005). However, TBI causes mitochondrial dysfunction leading to the generation of cytochrome c, and the stimulation of cell surface death receptors (e.g., by tumor necrosis factor, Fas ligands) that activate apoptotic effectors, including caspase-1 and caspase-3. The activation of these effectors can result in the cleavage (splitting of the chemical bond) of anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL) and endonucleases that are important to cell survival after injury (Zhang, et al., 1999). This, in turn, triggers the fragmentation of DNA, which leads to neuronal death and exacerbates cognitive and behavioural problems (Liou, Clark, Henshall, Yin, & Chen, 2003; Tashlykov, et al., 2007).

This has been supported in experimental and clinical research where increased concentrations of caspase-1 and caspase-3, together with DNA fragmentation, have been identified in rodent brains for up to three days after a TBI (Clark, et al., 1999; Clark, Kochanek, Watkins, et al., 2000; Yakovlev, et al., 1997). Elevated levels of caspase-3 have also been associated with poorer outcome and increased mortality after human TBI (Nathoo, et al., 2004). Moreover, cleavage of the anti-apoptotic protein Bcl-2 has been associated with poorer outcome in a clinical population and upregulation of this protein was predictive of improved outcome eighteen months after injury (Nathoo, et al., 2004).

In terms of pharmacological interventions, the caspase-3 inhibitor N-benzyloxycarbonyl-Asp-Glu-Val-Asp-fluoromethyl ketone, reduced caspase-3 activation and DNA fragmentation in rodents following TBI, although there was no associated improvement in functional outcome (Clark, Kochanek, Watkins, et al., 2000). In addition, the steroid hormone oestrogen reduced concentrations of caspase-3 and significantly increased expression of the anti-apoptotic protein Bcl-2 in rodents (Soustiel, Palzur, Nevo, Thaler, & Vlodavsky, 2005), suggesting that pharmacological treatments may be able to mediate some of the signalling pathways that are associated with apoptotic cell death after injury.

2.2 Summary

It is evident from research in the area of pharmacotherapy that there are many different agents that have been used to treat various biochemical changes after TBI in order to improve outcome. However it is not clear what treatments are the most effective. This is, in part, due to the large number of different treatments that have been investigated, each of which may target one or more of the biochemical changes that result from a TBI. Disparity in the findings between both animal and human research has also limited our understanding of both the treatments that are the most efficacious for reducing cognitive and behavioural

problems following TBI and the variables that affect treatment efficacy (e.g., drug dosage, injury severity, time-to-treatment).

A number of methodological variables have been identified as playing a potential role in the between-study differences in outcome following treatment with a pharmacological agent. These include differences in the timing of treatment (early or late), the severity of the TBI (mild, moderate, severe), sample size, as well as the drug dosage that is administered (Newburn, et al., 1999). In addition, the type of measure that is used to assess outcome, and the nature of the brain damage (focal or diffuse), as well as gender differences in outcome (Faden, 2001; Glenn & Wroblewski, 2005; Narayan, et al., 2002), may also contribute to discrepant findings within and between the animal and human literature. Treatment benefits may also be influenced by the research design that is used, with some designs (e.g., independent groups repeated measures, independent groups) providing better control for variables (e.g., spontaneous recovery, practice effects) that may be confounded with a treatment effect (Morris & DeShon, 2002).

One method for evaluating the efficacy of different pharmacological treatments is by conducting a meta-analysis. Meta-analyses objectively quantify the findings from different studies using a common measurement scale (i.e., effect size), thereby allowing a direct comparison of treatments both within and across animal and human research. In addition, by converting treatment effects to a common scale of measurement, it is possible to consolidate the findings from different studies and examine some of the methodological variables that may influence outcome. A synthesis of this research may help to clarifiy which treatments are the most efficacious and thereby improve the treatment of this condition.

2.3 Aims

The current research analyses and synthesises both experimental and clinical research literature that has investigated the impact of pharmacological treatments on outcome in adult

rodents and humans following TBI in order to consolidate the findings and identify the pharmacological treatments that are efficacious for reducing cognitive, behavioural and motor problems:

1. following experimental TBI in rodents (Chapter 3);
2. following early treatment (≤ 3 days post-injury) in a clinical population (Chapter 4);
3. following late treatment (≥ 4 weeks post-injury) in a human cohort (Chapter 5); and
4. compare the findings of Studies 1, 2, and 3, in order to clarify whether treatment benefits translate from rodents to humans, and across time in a human TBI population (i.e., acute to post-acute).

To this end three meta-analyses were conducted. *Chapter 3* synthesises the findings from the rodent literature. *Chapter 4* examines clinical research that has investigated treatments targeting early biochemical disruptions in the brain after a TBI. The final meta-analysis (*Chapter 5*) compares human research literature that examines treatments administered in the post-acute period to replace specific biochemicals in the brain.

Chapter 3 : Impact of pharmacological treatments on outcome in adult rodents after traumatic brain injury: A meta-analysis

The first study examined research that has investigated pharmacological treatments administered to adult rodents with the aim of identifying those treatments that have been efficacious in improving outcome after TBI. Many treatments have been investigated in this cohort, however, an objective comparison of their usefulness has been complicated by between study differences in the model of TBI (focal and diffuse) and the outcome measures that have been used to examine treatment benefits. A meta-analysis was therefore undertaken to quantify and compare the existing research, thereby allowing the relative efficacy of these treatments to be evaluated.

The following Chapter represents a manuscript that has been accepted for publication in the Journal of Psychopharmacology (In Press)[1]. This paper was written for a specialised target audience with an assumed knowledge of experimental research. Moreover, space restrictions precluded a discussion of the rational for evaluating rodent research and the different models of experimental TBI in the manuscript. These concepts are therefore addressed below.

A number of animal species have been used to examine the safety and efficacy of pharmacological treatments following TBI. The most popular of these are rodents, partly because they are small and inexpensive, which allows large numbers to be tested, thereby permitting multiple assessments of outcome to be examined (Cernak, 2005; Finnie, 2001). As

[1] For access to this paper go to Journal of Psychopharmacology:
Wheaton, P., Mathias, J.L., Vink, R. (2010). Impact of pharmacological treatments on outcome in adult rodents after traumatic brain injury: A meta-analysis. *Journal of Psychopharmacology*. (In Press)
URL: http://online.sagepub.com
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a result, most published research uses rodent models of TBI, which will be the focus of this Chapter.

A variety of different models of experimental TBI have been tested in rodents. The most commonly used of these are the controlled cortical impact model, the weight drop model, and fluid percussion injury models of TBI (Cernak, 2005). The controlled cortical impact model and the weight drop model both cause focal contusions and lacerations of the cortex beneath the site of the impact (Laurer, Lenzlinger, & McIntosh, 2000). In the former model a TBI is delivered to the brain using an air driven metallic piston, while in the later case damage results from a free-falling, guided weight impacting on the head (Cernak, 2005; Laurer, et al., 2000; Morales, et al., 2005).

A fluid percussion injury, on the other hand, results in diffuse cortical, subcortical and white matter damage at both the impact site and remote from the site of impact (Morales, et al., 2005). The two main types of fluid percussion injury are the central and the lateral models (Cernak, 2005). In both TBI models a pressure pulse of fluid is delivered to the intact dura of the brain, however in the central model pressure is applied around the midline, between the bregma and the lambda, whereas in the lateral model, injury is delivered over the left parietal bone between the bregma and the lambda (Cernak, 2005; Laurer, et al., 2000; Morales, et al., 2005).

One or more of the structural (e.g. cortical and/or white matter damage, changes to cerebral blood flow) and biochemical changes (e.g. altered ion homeostasis, neurotransmitter function) that result from a TBI have been observed in each of the abovementioned models. However, only experimental models such as the lateral and central fluid percussion injury models, which replicate both focal and diffuse damage, are able to reproduce the diverse range of injuries that are found in a clinical population. These models may therefore be better for examining treatment efficacy (Cernak, 2005).

Finally, treatment effects have been evaluated in experimental research using a variety of different measures. To simplify the presentation of the results, measures were categorised into those that examined cognition, behaviour, and motor function. However, it must be noted that measures that evaluate motor function are sometimes referred to in the experimental literature as 'behavioural' measures. Although most of the studies included in this meta-analysis used measures of cognition and motor function to examine treatment efficacy, a small number evaluated outcome in terms of anxiety/depression, aggression and zoosocial behaviour (e.g., habituation, stress, dominance). The behaviour category was therefore used to differentiate these later measures from those of cognition and motor function. It should be noted that some of the psychological consequences of TBIs (e.g. low self-esteem, suicidal thoughts, guilt) cannot be examined using animal models but are an added complexity in humans.

TITLE: Impact of pharmacological treatments on outcome in adult rodents after traumatic brain injury: A meta-analysis.

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Abstract

Pharmacological treatments have been widely investigated in pre-clinical animal trials to evaluate their usefulness in reducing cognitive, behavioural and motor problems after traumatic brain injury (TBI). However, the relative efficacy of these agents has yet to be evaluated, making it difficult to assess the strength of evidence for their use in a clinical population. A meta-analytic review of research (1980 – 2009) was therefore conducted to examine the impact of pharmacological treatments administered to adult male rodents after experimental TBI on cognitive, behavioural, and motor outcome. The PubMed and PsycInfo databases were searched using 35 terms. Weighted Cohen's *d* effect sizes, percent overlap, Fail Safe N statistics and confidence intervals were calculated for each treatment. Ninety-one treatments were evaluated in 223 pre-clinical trials, comprising 5988 rodents. Treatments that were investigated by multiple studies and showed large and significant treatment effects were of greatest interest. Of the sixteen treatments that were efficacious, six improved cognition, ten improved motor function and no treatment improved behaviour (depression/anxiety, aggression, zoosocial behaviour). Treatment benefits were found across a range of TBI models. Drug dosage and treatment interval impacted on treatment effects.

Keywords: pharmacological treatments, outcome, adult rodents, traumatic brain injury, meta-analysis

Running Title: Pharmacotherapy and outcome after rodent TBI

Introduction

A number of destructive biochemical events have been found to take place in the brain after sustaining a traumatic brain injury (TBI), including alterations in the synthesis and release of some neurotransmitters (Pappius, 1991), disruptions to ion homeostasis (Feng, Zhu, & Lu, 2004), the generation of toxic levels of excitatory amino acids (Faden, Demediuk, Panter, & Vink, 1989) and free radicals (Kline, Massucci, Ma, Zafonte, & Dixon, 2004; Pascual, et al., 2007) and the activation of inflammatory and immune response systems (Morganti-Kossmann, Satgunaseelan, Bye, & Kossmann, 2007). Pharmacological treatments have the potential to interrupt or compensate for some of these early biochemical changes (Arlinghaus, Shoaib, & Price, 2005), thereby improving cognitive and behavioural outcome (see Figure 3.1 of the Appendices for an outline of TBI secondary pathophysiology).

A variety of treatments have been developed for this purpose. These can be broadly categorised according to their primary mode of action (Ashley, 2004; Cooper, Bloom, & Roth, 2003; Webster, 2003), namely: serotonergic treatments, catecholamines, cholinergic agents, modulators of ion homeostasis, thyrotropin-releasing hormone analogues, vasodilators, opioids, anti-inflammatories, antidiuretics, modulators of free radical formation, steroids, modulators of amino acid activity, and growth factors. The safety and efficacy of new treatments for TBI are generally evaluated using experimental animal models of TBI before they are tested in clinical settings (Finnie, 2001; Finnie & Blumbergs, 2002). Rodent models, in particular, have been the mainstay of these investigations due to their small size and low cost (Finnie & Blumbergs, 2002).

Amongst the treatments that have proven to be efficacious for the treatment of cognitive (learning, memory) and motor function following TBIs in rodents are specific serotonergic (e.g., *5-HT1A receptor agonists*) (Cheng, Aslam, Hoffman, Zafonte, & Kline, 2007; Kline, Massucci, Marion, & Dixon, 2002; Kline, et al., 2007; Kline, Yu, Horvath,

Marion, & Dixon, 2001), catecholaminergic (e.g., *methylphenidate*) (Huang, Chen, Shohami, & Weinstock, 1999; Schmanke & Barth, 1997; Wagner, et al., 2007), and cholinergic agents (e.g., *rivastigmine*) (Chen, Shohami, Bass, & Weinstock, 1998; Chen Shohami, Constantini, & Weinstock, 1998). Similarly, modulators of ion homeostasis, such as certain calcium channel blockers (e.g., *S100B, ziconotide, nimodipine*) and a sodium channel blocker (*riluzole),* have improved cognition and/or motor performance (Wahl, Renou, Mary, & Stutzmann, 1997), although *nimodipine* was only associated with short-term recovery (Hinson, Lambert, & LeVere, 1996). Improvements in cognition have also been found with anti-inflammatory steroids (i.e. *progesterone, raloxifene*) (Kokiko, Murashov, & Hoane, 2006; O'Connor, et al., 2007; Shear, Galani, Hoffman, & Stein, 2002) and thyrotropin-releasing hormone analogues (i.e. *TRH35b; 1-ARA-53a***).** In addition, the inhibition of excitatory amino acids using the non-competitive NMDA antagonist *dextrorphan* (Faden, et al. 1989) as well as the glutamate release inhibitors magnesium sulphate and *magnesium chloride* have been shown to improve overall neurological outcome (Barbre & Hoane, 2006; Heath & Vink, 1998a, 1999), and *magnesium sulphate* has been found to reduce depression and anxiety (Fromm, Pharm, Heath, Vink, & Nimmo, 2004). Furthermore, a number of agents have been shown to promote plasticity and regeneration (anti-Nogo-A, inosine; nerve growth factor) and reduce cognitive deficits (anti-Nogo-A, nerve growth factor) after TBI (Dixon, Flinn, Bao, Venya, & Hayes, 1997; Marklund, et al., 2007; Sinson, Perri, Trojanowski, Flamm, & McIntosh, 1997; Smith, et al., 2007).

However, there are also numerous other treatments that have either not been effective in improving cognition or motor function, including the inhibitor of sodium and magnesium exchange *amiloride* (Turner, Van den Heuvel, & Vink, 2004) and the thyrotropin-releasing hormone *TRH* (Okuyama, et al., 1997), or have actually worsened outcome (i.e. dextrose, the NOS inhibitors aminoguanidine, and L-NIL) (Shapira, Artru, Qassam, Navot, & Vald, 1995;

Sinz, et al., 1999). Moreover, there are also treatments that have only proven to be beneficial when they are administered before, not after, a TBI (i.e. the NMDA receptor antagonists MK-801 and the muscarinic receptor antagonist scopolamine) (Hamm, O'Dell, Pike, & Lyeth, 1993; McIntosh, Vink, Soares, Hayes, & Simon, 1989).

While the research examining treatments for TBI in animals is extensive, it has not yet been adequately consolidated in order to evaluate the evidence-base for treatments that have undergone pre-clinical trials. This is partly due to the large number of different treatments that have been researched and to the range of measures that have been used to evaluate treatment efficacy (tests of cognition, motor skills, behaviour). An added complexity is that this research has used different models of experimental TBI (i.e. weight drop, controlled cortical impact, lateral and central fluid percussion injury models) and different strains of rodents (i.e., Wistar, Sprague Dawley, Long-Evans), the impact of which is unclear (Tan, Quigley, Smith, & Hoane, 2008; Vales, Bubenikova-Valesova, Klement, & Stuchlik, 2006; Zamudio, Fregoso, Miranda, De La Cruz, & Flores, 2005). Moreover, there are a number of methodological variables (e.g., injury severity, injury-to-treatment interval, drug dosage) that further complicate the picture (Narayan, Michel, & Group, 2002). Finally, small sample sizes may affect the ability to detect a significant treatment effect, with statistically significant results being more likely in large samples (Tilley, 1996). Together, these factors make it difficult to evaluate the efficacy of treatments that have undergone pre-clinical testing with rodents.

One solution to this is to complete a meta-analysis, which uses effect sizes to provide an objective and quantitative means by which to standardize the research findings, thereby enabling them to be directly compared. The current study therefore undertook a meta-analysis of pharmacological treatments that have been administered to rodents following experimental TBI with the aim of determining their relative impact on outcome.

Method

An exhaustive search was undertaken of the PubMed Central and PsycINFO electronic databases from January 1980 to February 2009 to identify studies that examined pharmacological treatments for cognitive, behavioural and motor problems in rodents after TBI. The key search terms (N = 35) were kept broad in order to capture all potentially relevant articles and are provided in Table 1. In addition, the reference lists of all of the retrieved studies were examined.

For a study to be included in this meta-analysis, it had to meet a number of inclusion criteria the details of which are set out in Table 2. The initial literature searches identified 4,661 articles, many of which only broadly related to the current study (refer to Figure 3.2 of the Appendices for details of electronic database searches). A preliminary application of the inclusion criteria to the titles and abstracts of these studies identified 260 articles that warranted closer examination. Retrieval of the full-text versions of these papers and a re-application of the inclusion criteria revealed that 135 did not meet all of the study criteria**.** Fifty-three of the remaining 125 studies did not provide sufficient data for the calculation of an effect size. Although written requests for additional data were made in all cases, only 24 provided the data needed for inclusion, and 29 were excluded because the authors did not respond or could not be located, leaving 96 studies.

Table 1: Key search terms used in database searches

Traumatic brain injury	**Pharmacology**	
traumatic brain injury	pharmacology	drug therapy
TBI	pharmacological treatment	pharmacotherapy
head injury	drug treatment	drug
head injuries	magnesium or Mg	substance P
brain injury	cyclosporin A or CyA	progesterone
brain injuries	oestrogen	dexanabinol
head trauma	dexamethasone	dynorphin
concussion	methylphenidate	amitriptyline
post-concussion	phenelzine	opiate
post concussion	glutamate	calcium
post-concussion syndrome	free radical scavenger	NMDA
post concussion syndrome	treatment	

Table 2: Criteria for inclusion/exclusion of studies

Inclusion Criteria	Excluded Studies
a) was published in a journal	non-published studies and dissertations
b) was published in English	
c) had a TBI treatment group that was treated with a pharmacological agent and TBI control group that was administered a placebo following injury	involved non-impact (e.g., cortical ablation) or penetrating TBI (e.g., missile-induced TBI) did not administer a pharmacological treatment or used another type of treatment (e.g., hypothermia, cell transplants, environmental enrichment) only treated rodents with a pharmacological agent prior to the induction of a TBI did not have a TBI injured control group (e.g., only healthy or sham injured controls)
d) the TBI control group was matched to the treatment group on the basis of age or weight and injury severity. Note : where a study reported the magnitude of injury but did not give specific details of the level of injury severity (e.g., mild, moderate, or severe) this was identified as a limitation to the study's quality	

Cont'd

Table 2 Cont'd

Inclusion Criteria	Excluded Studies
e) male rodents (rat or mouse) were used to evaluate treatment effects	samples that included intact female rodents. animals that were genetically or surgically altered (e.g., gene deficiency, ovariectomy) examined other types of animals (e.g., sheep, cat, dog etc.)
f) both groups were administered measures of cognition (memory), behaviour (depression/anxiety, aggression, zoosocial behaviour [e.g., habituation, stress dominance]) and/or motor function to assess outcome	studies using only biochemical or physiological measures of treatment efficacy
g) the results were reported in a format that enabled the calculation of an effect size (i.e. means, standard deviations, *t* tests, *F* ratios from a one-way analysis of variance, or exact *p* values) or authors provided this information in response to a written request	performed other types of multivariate parametric analyses, non-parametric statistical tests, or where data was presented in graphical form
h) adult animals were used. Where age was not reported, a study was deemed eligible if the minimum weight of the animals was consistent with that of an adult rat or mouse	used juvenile or immature rodents.

When conducting a meta-analysis it is important to ensure that the participants in each study are independent of those used in other studies (Hunter, Schmidt, & Jackson, 1982; Rosenthal, 1995). Moreover, treatment effects may be influenced by drug dosage which, if averaged, may conceal differential effects. For these reasons, the studies reported in 45 articles were separated into two or more studies because they used different samples to investigate different treatments, dosages, drug combinations, and/or different injury-to-treatment times, or reported multiple independent experiments within a single article (see Table 3.A of the Appendices for details of separated studies). This increased the number of independent studies by 127. Thus, in total, the data came from 223 studies that examined 91 pharmacological treatments following experimental TBI in rodents. An examination of the bibliographies of all retrieved articles did not identify any additional studies. Demographic and bibliographic details for each study, together with the measures that were used to assess efficacy, are provided in Table 3.B of the Appendices.

Data Preparation

There were some cases where outcome measures (cognitive, behavioural, motor) were administered on multiple occasions during or following treatment. If these data were averaged, it may have altered the resulting effect size (e.g., where there are large treatment effects early in a study and small effects at the end, the average would be larger than for a study where only a final post-treatment score was reported). Because not all studies assessed outcome repeatedly, only data from the final session at the end, or after completion, of the treatment were used to calculate effect sizes.

Some basic transformations were needed to standardize the data before they could be analysed. In the first instance, standard errors were transformed to standard deviations to allow the calculation of effect sizes. Secondly, the data for time-to-treatment and time-to-

testing were transformed to ensure a common scale of measurement (minutes and hours, respectively).

Each treatment was categorised into a chemical group and primary method of action, the details of which are summarized in Table 3.C of the Appendices. This system was adopted to simplify the presentation of data and is not intended to imply that the method of action of these drugs is limited to a single chemical group. Importantly, the presentation of data in this way does not alter the results because the effect sizes for different treatments were not combined.

Statistical Analysis

Cohen's *d* effect sizes were calculated to measure the difference between two means (treatment and control groups) divided by the pooled standard deviation (Zakzanis, 2001). Effect sizes were calculated in such a way that a positive *d* indicated that treatment improved outcome. Cohen (1977, 1992) defines a small effect as $d = .2$, a moderate effect as $d = .5$ and a large effect as $d = .8$, where an effect size of .5 indicates that there is a difference of one half of a standard deviation between the groups. If means and standard deviations were not provided for a study, *t* values, one-way *F* statistics or exact *p* values were converted to *d* using the formula provided by Zakzanis (2001). Where exact *p* values were reported, the appropriate *t* statistic was derived from a table provided by (Lipsey & Wilson, 2001) and this measure was used to calculate *d*.

A multistage process was used when calculating an effect size for each treatment. The first step involved calculating an effect size for each measure of outcome that was used by a study. If a study provided multiple scores for a measure, an effect size was calculated for each individual score and then averaged to provide a single score for that measure. The effect sizes obtained from different studies that examined a given treatment using the same measure were then averaged to determine treatment effects.

The reliability of an effect size is affected by the size of the sample from which it is derived, making it important to weight effect sizes before they are averaged (Hunter & Schmidt, 2004; Lipsey & Wilson, 2001; Rothstein, Sutton, & Borenstein, 2005). Therefore, an overall weighted mean effect size (d_w) was calculated by weighting each of the effect sizes from individual studies by the inverse variance (i.e., the inverse of the squared standard error) and then averaging them (Hedges & Olkin, 1985). In addition, as more confidence can be placed in the findings of high quality studies than those of poor quality studies, all studies that were included in the current meta-analysis were categorised according to their methodological quality. Two independent raters (PW and a senior undergraduate student) assessed the methodological quality of each study using a twenty-item scale (e.g., randomisation, assessor blinding, matching of treatment and control groups) that was based on the rating scale developed by (Sindhu, Carpenter, & Seers, 1997) (see Appendix 3.A for the quality rating tool). A consensus rating score between zero (met none of the quality criteria) and twenty (met all of the quality criteria) was then used to rank studies into one of five equal interval groups (5 = highest quality, 4 = high quality, 3 = moderate quality, 2 = low quality, 1 = lowest quality) (see Appendix 3.B for specific details of quality score groupings).

Percentage overlap scores (%OL) were also calculated (Zakzanis, et al., 1999) to measure the extent to which the test scores from the two groups overlap, where a $d = 0$ signifies 100% overlap and a $d = 4$ indicated almost complete discrimination (2.3% overlap). Ninety-five percent confidence intervals (95% CI) were additionally calculated for all effect sizes using the method described by Lipsey and Wilson (2001) in order to provide a measure of the range and precision of the mean effect size estimate and to determine statistical significance (i.e., a 95% CI that does not include zero indicates a significant difference between the treatment and control groups). Finally, fail safe Ns (N_{fs}) were calculated to address any bias caused by the tendency to publish studies with significant findings. The fail

safe N statistic provides a measure of the number of unpublished studies with small treatment effects (i.e., $d \leq .2$) that are needed to reduce an effect size to .2 and thereby call the current findings into question (Lipsey & Wilson, 2001).

Data Interpretation

Mean weighted Cohen's *d* effect sizes (Mean d_w, SD, 95% CI, N_{fs}) were calculated for each of the cognitive, behavioural and motor tests that were used to evaluate the 91 treatments. The conclusions of this meta-analysis are based on the combined interpretation of these statistics. It is argued that we can be more confident that a treatment has improved outcome if there is a large and significant positive difference between groups (i.e., $d_w \geq .8$, 95% CI $\neq 0$) and if it is unlikely that there would be sufficient unpublished studies showing small treatment effects to call the current findings into question ($N_{fs} \geq 3$). In addition, findings that are based on high quality studies are preferable to those of low quality studies because they control for more potentially confounding variables. Finally, while effect sizes that are based on more than one study are thought to provide a more reliable measure of group differences, many experimental treatments have only been investigated by a single study. Thus, the results for treatments that were examined by both multiple studies and a single study are considered, with those that were examined by multiple studies examined first followed by those that were investigated by single studies.

The results are grouped according to chemical group. Cognitive, behavioural and motor outcomes are then reported for each treatment within these groups ordered by number of studies (multiple studies then single studies) and rank ordered by effect size (largest to smallest). Those treatments that produced measurable ($d_w \geq .8$) and significant (95% CI $\neq 0$) treatment effects; are unlikely to be influenced by publication bias (large N_{fs}), and have been investigated by multiple high quality studies ($N_{Studies} > 1$), are of greatest interest to this analysis.

Results

Of the 223 studies that were included in this meta-analysis, 131 (59%) examined rats, the majority of which were Sprague-Dawley rats, and 92 (41%) examined mice. Data was analysed for a total of 5988 male rodents with an average sample size of 13 animals in the treatment groups (SD = 6) and 14 in the control groups (SD = 8) (refer to Table 3 for overall data). Of the 118 studies that provided injury severity, 66 reported a moderate injury, 28 a mild injury, and 24 a severe injury. Over half of the animals were injured using the weight drop model of experimental injury ($N_{studies}$ = 113), with the remainder using the controlled cortical impact injury ($N_{studies}$ = 51), the lateral fluid percussion injury ($N_{studies}$ = 46), or the central fluid percussion injury ($N_{studies}$ = 13) models. The majority of studies (79%; $N_{studies}$ = 175) administered treatment at or within one hour of injury, while 20% ($N_{studies}$ = 45) initiated treatment beyond one hour post-injury, and three did not provide this information (1%). Few studies reported adverse events (7%) and no studies evaluated drug concentrations in target brain regions. Most studies were of high to very high quality (82%).

As Table 3 shows, few studies reported the animal's mean age in weeks (17%), therefore, we also used minimum weight to classify the rodents as adults. On average, animals were treated within six hours of injury and underwent testing within two weeks of treatment. A total of thirty-six measures were used to evaluate treatment effects, including four measures of cognition (Morris Water Maze, Object Recognition Test, Memory Task, Freezing Response), five measures of behaviour (Open Field Test, Elevated Plus Maze, Spontaneous Motor Activity, Exploratory Activity, Emotional Activity) and twenty-seven measures of motor function (e.g., Rotarod, Grip Test). The complete set of results are reported in Tables 3.D to 3.R of the Appendices. Only those meeting the abovementioned criteria are summarised in detail. Unless stated otherwise, the results refer to studies of rats.

Table 3: Animal and treatment data for the TBI treatment and control groups

	Total (overall data for treatment and control groups)				
	$N_{studies}$	$N_{animals}$	M	SD	Range
Participants	223	5988	27	13	6 - 71
Age (weeks)	38	1009	11	3	6 - 16
Weight (grams)	184	4918	190	132	20 - 420
Time from injury (hours)	220	5928	6	26	<1 - 264
Time to testing (days)	208	5386	12	25	<1 - 25

Note: $N_{animals}$ = total number of rodents contributing to M = mean, SD – standard deviation and Range; $N_{studies}$ = total number of studies contributing to M = mean, SD = standard deviation and Range; Time from injury = time from injury to treatment in hours; Time to testing = time from treatment to cognitive, behavioural or motor testing in days.

Treatment Effects

Serotonergic treatments

Although four high to very high quality studies examined the impact of a single serotonergic agent, the 5-HT1A receptor agonist *8-OH-DPAT*, after a controlled cortical impact injury (see Tables 3.B and 3.D of the Appendices), this treatment resulted in large but non-significant changes in cognition (Morris Water Maze), and so did not meet the criteria for treatment efficacy.

Catecholaminergic treatments

In total, twenty-nine studies investigated eight catecholamines in relatively small samples (i.e., $N_{Animals} < 50$) using the weight drop, the controlled cortical impact, or the

central fluid percussion injury model of TBI (see Appendices Table 3.E). Only four of these, one of which used mice (*Rasagline*), showed large and significant treatment effects (refer to Table 4). *Rasagline* (selective MAO-B inhibitor) and *L-deprenyl* (MAO-B inhibitor) were associated with notable improvements in spatial learning and memory, as measured by the Morris Water Maze based on single studies of high to very high quality, while a large improvement in gross motor function (Beam Balance) was found by one of the two studies that investigated treatment with the catecholamine transport inhibitor *methylphenidate* (Ritilan). Four high quality studies also examined treatment with *haloperidol* (dopamine 2 receptor antagonist) (refer to Table 3.E of the Appendices), one of which showed poorer motor activity and co-ordination on the beam walk task (see Table 4).

None of the remaining catecholamines (*risperidone* [dopamine 2 receptor and serotonin antagonist], combined treatment with *rasagaline* and *scopolamine*, *SCH 23390* [dopamine 1 receptor antagonist], *sulpiride* [dopamine 2 receptor antagonist], combined treatment with *sulpiride* and *SCH 23390* and the D2 receptor agonist *apomorphine*) met the study criteria for improved outcome (Appendices Table 3.E).

Cholinergic treatments

While five cholinergic treatments were examined by a total of twenty-eight studies that used either a central fluid percussion or weight drop model of TBI injury (refer to Table 3.F of the Appendices), only two showed a large and significant treatment benefits (see Table 4). A marked improvement in spatial learning and memory (Morris Water Maze) was found by two high quality studies that investigated treatment with the partial muscarinic M1 agonist and M2 antagonist *LU 25-109-T*, albeit in a small sample. Two high quality studies that investigated the acetylcholinesterase inhibitor *ENA 713* in mice also showed a large and significant treatment benefit for motor function (NSS) after severe TBI.

Table 4: Weighted mean effect sizes for serotonergic, catecholamine, cholinergic, calcium agents, TRH analogues, vasodilators, and opioids with large treatment effects.

Drug and Measure	Outcome	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
CATECHOLAMINERGIC TREATMENTS														
Rasagiline														
Morris Water Maze*	Cognitive	1	16	5	severe	WD	2.02		.70	3.34	9	19	high	Huang, Chen et al, 1999
Haloperidol														
Beam Walk	Motor	1	24	1,440	not specified	CCI	-1.49		-2.46	-0.52	7	29	high	Hoffman, Cheng et al, 2008
Methylphenidate														
Beam Balance	Motor	1	32	1,440	not specified	CCI	1.48		.63	2.33	6	29	moderate	Wagner, Kline et al, 2007
L-deprenyl														
Morris Water Maze	Cognitive	1	15	1,440	moderate	Central FPI	1.01		.04	1.98	4	45	highest	Zhu, Hamm et al, 2000
CHOLINERGIC TREATMENTS														
LU 25-109-T														
Morris Water Maze	Cognitive	**2**	16	**1,440**	moderate	Central FPI	**1.27**	.88	**.16**	**2.55**	12	35	high	Pike & Hamm, 1997
ENA 713														
NSS*	Motor	**2**	30	**5**	severe	WD	**1.07**	2.40	**.72**	**2.81**	10	41	highest	Chen, Shohami et al, 1998

Cont'd

Table 4 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
MODULATORS OF CALCIUM HOMEOSTASIS														
SNX-185														
Morris WaterMaze	Cognitive	**3**	15	**5**	not specified	Lateral FPI	**2.17**	1.21	**1.06**	**4.15**	32	16	high	Lee, Galo et al, 2004
Ziconotide														
Beam Walk	Motor	1	17	180	moderate	WD	1.70		.50	2.90	8	25	highest	Berman, Verweij et al, 2000
Inclined Plane Test	Motor	1	17	180	moderate	WD	1.42		.29	2.55	6	32	highest	Berman, Verweij et al, 2000
Radial Arm Maze	Motor	1	17	180	moderate	WD	1.43		.30	2.56	6	32	highest	Berman, Verweij et al, 2000
Beam Balance	Motor	1	17	180	moderate	WD	1.17		.09	2.24	5	38	highest	Berman, Verweij et al, 2000
THYROTROPIN-RELEASING HORMONE ANALOGUES														
TRH 35b														
Morris Water Maze	Cognitive	1	22	30	moderate	Lateral FPI	5.70		3.14	8.25	28	2	high	Faden, Knoblach et al, 2003

Cont'd

Table 4 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
YM 14673														
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.43		.43	2.43	6	32	high	Faden, 1993
YM 14673 + Nalmefene														
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.33		.35	2.31	6	35	high	Faden, 1993
2-ARA-53a														
Composite Neuroscore	Motor	1	31	30	moderate	Lateral FPI	.93		.16	1.70	4	48	high	Faden, Fox et al, 1999
VASODILATORS														
SB 209670														
NSS	Motor	**4**	12	**15**	not specified	WD	**1.94**	1.85	**1.03**	**4.81**	38	21	moderate	Barone, Ohlsten et al, 2000
SB 234551														
NSS	Motor	**2**	12	**15**	not specified	WD	**1.56**	.97	**.31**	**3.18**	15	45	moderate	Barone, Ohlsten et al, 2000
OPIOIDS														
Nalmefene + Dextrorphan														
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.25		.29	2.21	5	35	high	Faden, 1993

Note: WD = Weight drop injury; CCI = controlled cortical impact injury; Central FPI = central fluid percussion injury; Lateral FPI = lateral fluid percussion injury ; NSS = Neurological Severity Score

Note: Large treatment effects $N_{studies}$ >1 are presented in bold print

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI

There were no other cholinergic treatments (*scopolamine*, *THA* [Tetrahydroaminoacridine], *mecamylamine*, combined treatment with *ENA 713* and *mecamylamine*, and combined treatment with *ENA 713* and *scopolamine*) that showed any sizeable treatment effects after a moderate or severe TBI (refer to Table 3.F, of the Appendices).

Modulators of calcium homeostasis

Seven small scale studies ($N_{Animals} \leq 25$) investigated treatment with four modulators of ion homeostasis (refer to Appendices, Table 3.G). However, only two calcium channel blockers met the study criteria for improved outcome (see Table 4) using either a lateral fluid percussion or weight drop model of experimental TBI. A large to very large improvement in spatial learning and memory (Morris Water Maze) was found by the three high quality studies that treated rodents with the N-type calcium channel blocker *SNX-185*. In addition, a single very high quality study that investigated treatment with *ziconotide* (N-type calcium channel blocker) after a moderate TBI showed a marked improvement in motor function on the Beam Walk, the Inclined Plane Test, the Radial Arm Maze, and the Beam Balance task. Neither the non-selective calcium binding protein *S100B* nor the Maxi-K channel opener *BMS-204352* improved cognition or motor function (refer to Table 3.G of the Appendices).

Thyrotropin-Releasing Hormone Analogues

There were four high quality studies that investigated the effects of four treatments after a lateral fluid percussion injury (refer to Table 4 and Table 3.H of the Appendices). All showed large to very large treatment benefits when administered within thirty minutes of an injury. A very large improvement in spatial learning and memory (Morris Water Maze) was found by one study when *TRH 35b* (TRH analogue) was administered after a moderate TBI. Single studies that examined *YM 14673* (TRH analogue), combined treatment with *YM 14673*

and *nalmefene* (non-selective opioid antagonist), or *2-ARA-53a* (TRH analogue) also showed improved motor outcome and balance on the Composite Neuroscore.

Vasodilators

Large treatment benefits were found by the six studies that examined two endothelin-A receptor antagonists in small samples of rodents ($N_{Animals}$ = 12) (see Table 4 and Appendices, Table 3.I). When treatment was administered within fifteen minutes of a weight drop injury of unspecified severity, functional status (balance, reflexes, and alertness) and motor activity (as measured by the NSS) was improved in four studies of moderate quality that investigated *SB 209670* and two that investigated *SB 234551*.

Opioids

Four moderate to high quality studies investigated four opioids after a lateral fluid percussion, weight drop or controlled cortical impact injury (refer to Table 3.J of the Appendices). A single study that examined combined treatment with *nalmefene* (non-selective opioid antagonist) and *dextrorphan* (non-competitive NMDA antagonist) showed a marked improvement in motor outcome and balance on the Composite Neuroscore (see Table 4). Neither *nalmefene* (non-selective opioid antagonist) alone nor *nor-BNI* (selective kappa-opioid antagonist) significantly improved motor function (Composite Neuroscore, Morris Water Maze) in single high quality studies. The non-selective opioid agonist *morphine* showed a small but non-significant negative treatment effect for memory and learning on the Morris Water Maze in mice following a mild TBI in a study of moderate quality (refer to Appendices, Table 3.J).

Anti-inflammatories

A total of eighteen studies investigated the effects of nine anti-inflammatory treatments on cognition and motor function in rodents after an injury of moderate, severe or unspecified severity (see Appendices, Table 3.K). Six of these treatments showed large and

significant improvements to outcome when administered within 24 hours of a lateral fluid percussion, controlled cortical impact or weight drop induced TBI.

Of the five anti-inflammatories that were investigated by multiple studies four markedly improved outcome (refer to Table 5). There were sizeable and significant improvements in sensorimotor function and fine motor co-ordination (Forelimb Placing Test) observed in two high quality studies after treatment with *B3* (vitamin/anti-inflammatory). In addition, two studies of moderate quality showed improved memory (Morris Water Maze) and motor outcome (Composite Neuroscore) in mice with *C1-INH* (C1 esterase inhibitor). A further six studies investigated two HMG-CoA reductase inhibitors, two of which examined treatment with *simvastatin* and four investigated *atorvastatin*. Overall, the quality of these studies was high. *Simvastatin* and *atorvastatin* both showed large to very large treatment benefits for memory and learning on the Morris Water Maze.

Another four anti-inflammatory agents that were each investigated by single studies also showed large treatment benefits (see Table 5). Specifically, large and significant improvements in neurological and motor function were found for *B3* (Tactile Removal Test), the pro-inflammatory complement inhibitor *VCP* (Lateral Left Pulsion, Tactile Placing, Right Lateral Pulsion), *atorvastatin* (Modified NSS, Corner Test), and in mice with the specific interleukin-18 inhibitor *IL-18BP* (NSS) when treatment was administered within twenty-four hours of injury. There were no significant treatment benefits found on measures of motor function or cognition for *minocycline HCI* (tetracycline antibiotic, antioxidant, anti-inflammatory), *COG 1410* (apolipoprotein E-based peptide) or *IL-10* (cytokine synthesis inhibitor) (refer to Appendices, Table 3.K). In combination these results suggest that anti-inflammatory treatments may improve cognition and motor outcome following TBI in rodents.

Table 5: Weighted mean effect sizes for anti-inflammatories, immunosuppressants, modulators of free radical formation, and steroids with large treatment effects.

Drug and Measure	Outcome	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
ANTI-INFLAMMATORIES														
B3 (Nicotinamide)														
Forelimb Placing Test	Motor	**2**	22	**15**	moderate	Lateral FPI	**4.09**	2.68	**2.96**	**7.37**	40	2	high	Hoane, Tan etal, 2006
Tactile Removal Test	Motor	1	18	15	not specified	CCI	3.10		1.51	4.69	15	7	moderate	Hoane, Akstulewicz et al, 2003
Simvastatin														
Morris Water Maze	Cognitive	**2**	20	**1,440**	not specified	CCI	**2.49**	2.76	**1.96**	**5.54**	24	13	moderate /high	Lu, Qu et al, 2007
Atorvastatin														
Morris Water Maze	Cognitive	**3**	17	**1,440**	not specified	CCI	**1.55**	1.45	**.19**	**2.90**	34	27	high	Lu, Qu et al, 2007; Lu, Goussev et al, 2004; Lu, Mahmood et al, 2004
Modified NSS	Motor	1	20	1,440	not specified	CCI	2.43	-	1.12	3.74	11	13	high	Lu, Goussev et al, 2004
Corner Test	Motor	1	20	1,440	not specified	CCI	1.41	-	.37	2.45	6	32	high	Lu, Goussev et al, 2004
C1-INH														
Composite Neuroscore*	Motor	**2**	24	**10-60**	not specified	CCI	**1.30**	.42	**.39**	**2.27**	12	35	moderate	Longhi, Perego et al, 2009
Morris Water Maze*	Cognitive	**2**	24	**10-60**	not specified	CCI	**.91**	.61	**.08**	**1.86**	8	48	moderate	Longhi, Perego et al, 2009

Cont'd

Table 5 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
VCP														
Lateral Left Pulsion	Motor	1	10	5	severe	Lateral FPI	3.56		1.36	5.77	17	4	low	Pillay, Kellaway et al, 2007
Tactile Placing	Motor	1	10	5	severe	Lateral FPI	3.18		1.14	5.23	15	6	low	Pillay, Kellaway et al, 2007
Right Lateral Pulsion	Motor	1	10	5	severe	Lateral FPI	2.37		.64	4.11	11	13	low	Pillay, Kellaway et al, 2007
IL-18BP														
NSS*	Motor	1	34	60	not specified	WD	1.00		.25	1.75	4	45	high	Yatsiv, Morganti-Kossmann et al, 2002
IMMUNOSUPPRESSANTS														
Cyclosporin A														
Composite Neuroscore*	Motor	1	24	15	severe	CCI	3.02		1.64	4.40	14	7	high	Mybe, Singh et al, 2009
MODULATORS OF FREE RADICAL FORMATION														
CDP-Choline														
Composite Neuroscore	Motor	**3**	16	**5**	moderate	CCI	**1.76**	1.71	**1.04**	**4.19**	25	23	high	Dempsey & Rao, 2003
Beam Balance	Motor	1	20	1,440	not specified	CCI	.97		.01	1.93	4	45	high	Dempsey & Rao, 2003

Cont'd

Table 5 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
1400W														
Global Neuroscore	Motor	**2**	28	**5-360**	not specified	Lateral FPI	**.98**	.42	**.20**	**1.88**	9	45	high	Dixon, Xiecheng et al, 1997
Bemithyl														
Elevated Plus Maze	Behaviour	1	20	not specified	moderate	CCI	16.49		9.83	23.15	82	2	moderate	Zarubina, 2003
Exploratory Activity	Behaviour	1	20	not specified	moderate	CCI	7.60		4.43	10.77	37	2	moderate	Zarubina, 2003
Spontaneous Motor Activity	Behaviour	1	20	not specified	moderate	CCI	5.54		3.12	7.95	27	2	moderate	Zarubina, 2003
Open Field Test	Behaviour	1	20	not specified	moderate	CCI	1.41		.35	2.47	6	32	moderate	Zarubina, 2003
DETA/NONOate														
Modified NSS	Motor	1	36	1,440	severe	CCI	3.40		2.09	4.71	16	5	high	Lu, Mahmood et al, 2003
Corner Test	Motor	1	36	1,440	severe	CCI	2.53		1.45	3.61	12	11	high	Lu, Mahmood et al, 2003
PBN														
Combined Neuroscore	Motor	1	17	30	moderate	Lateral FPI	1.66		.47	2.85	7	25	high	Marklund, Clausen et al, 2001
B2														
Tactile Removal Test	Motor	1	15	15	not specified	CCI	1.60		.36	2.84	7	27	high	Hoane, Wolyniak et al, 2005

Cont'd

Table 5 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
DMSO														
Grip Test*	Motor	1	16	5	moderate	WD	1.27		.15	2.40	5	35	high	De la Torre, 1995
Murine IgG														
Composite Neuroscore	Motor	1	20	60	moderate	Lateral FPI	1.23		.22	2.23	5	38	high	Knoblach & Faden, 2002
Anti-ICAM														
Composite Neuroscore	Motor	1	24	60	moderate	Lateral FPI	1.19		.27	2.12	5	38	high	Knoblach & Faden, 2002
L-NIL														
Global Neuroscore	Motor	1	40	360	not specified	Lateral FPI	1.19		.48	1.91	5	38	moderate	Louin, Marchand-Verrecchia et al, 2006
Inosine														
Staircase Test	Motor	1	16	5	not specified	CCI	1.15		.04	2.25	5	38	moderate	Smith, Lunga et al, 2007
STEROIDS														
Raloxifene														
Adhesive Removal Test	Motor	1	16	15	not specified	CCI	1.14		.04	2.24	5	41	high	Kokiko, Murashov et al, 2006

Note: WD = Weight drop injury; CCI = controlled cortical impact injury; Central FPI = central fluid percussion injury; Lateral FPI = lateral fluid percussion injury ; NSS = Neurological Severity Score.

Note: Large treatment effects $N_{studies}$ >1 are presented in bold print

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI

Antidiuretics

Two antidiuretics (V-1880 *and V-2381*) were each investigated in single high quality studies of mice (see Table 3.L of the Appendices). When treatment was administered within three minutes of a controlled cortical impact injury, neither of these agents showed a significant improvement in motor outcome as measured by the Beam Walk task.

Immunosuppressants

There were two immunosuppressants that were examined in mice by three high quality studies after a controlled cortical impact or weight drop injury (refer to Appendices, Table 3.M). One study showed a marked improvement in motor function as measured by the Composite Neuroscore with the cyclophilin binder *cyclosporine A* after severe TBI (see Table 5). No sizeable treatment effect was found for motor activity (NSS) in two small-sample studies (N =13) that investigated the serine/threonine kinase inhibitor *rapamycin*.

Modulators of Free Radical Formation

Overall, seventeen modulators of free radical formation were examined by thirty-eight small to moderate scale studies ($N_{Animals}$ 12 to 65) using lateral fluid percussion, controlled cortical impact, or a weight drop models of TBI injury (refer to Table 3.N of the Appendices). Eleven treatments showed large to very large benefits (see Table 5).

Marked improvements in neurological and sensorimotor function (Composite Neuroscore) were evident in multiple studies of high quality after treatment with *CDP-choline* (Composite Neuroscore) and the NOS inhibitor *1400W* (Global Neuroscore) (refer to Table 5). A further ten treatments that were each examined by single studies ranging in quality from moderate to high also showed large benefits. In particular, *bemithyl* improved spontaneous motor activity and behaviour (Elevated Plus Maze, Exploratory Activity, Spontaneous Motor Activity, Open Field Test). A very large improvement in motor function was also apparent for *DETA/NONOate* on the modified NSS and Corner Test and on the

Composite Neuroscore for *Murine IgG* and *Anti-ICAM*. Benefits to motor activity were also observed with *CDP-choline* (Beam Balance task), *PBN* (Combined Neuroscore), *B2* (Tactile Removal Test), *inosine* (Staircase Test), *L-NIL* (Global Neuroscore), and in mice with *DMSO* (Grip Test) (see Appendices, Table 3.N).

The remaining six free radical scavengers did not show any marked treatment benefits in either single (*S-PBN*, *AG*, *7-NI*) or multiple studies (*L-NAME, PenME, melatonin*). Overall, this indicates that free radical scavengers may reduce behavioural and motor problems in rodents following TBIs that vary in severity.

Steroids

Two steroid treatments were examined by four studies following controlled cortical impact injuries (refer Appendices, Table 3.O); three investigated the progesterone receptor modulator and antioxidant *progesterone* and one examined the selective oestrogen receptor modulator *raloxifene*. All used small samples ($N_{Animals} < 20$). While *raloxifene* showed large improvements in sensorimotor function (Adhesive Removal Test) (see Table 5), based on a study of acceptable quality, neither *raloxifene* nor *progesterone* improved cognition or behaviour (Appendices).

Modulators of Amino Acid Activity

In all, 29 studies have examined 14 modulators of amino acid activity using one of four models of experimental TBI (controlled cortical impact, weight drop, lateral or central fluid percussion injury model) (see Table 3.P of the Appendices). Only nine of these treatments improved outcome. The three treatments that were investigated by two studies each showed large treatment effects (refer to Table 6). There were marked and significant improvements in fine motor co-ordination and neurological function observed after treatment with *magnesium sulphate* (Rotarod), and *HU-211* (NSS) while treatment with *DCS* improved

spatial learning and memory (Morris Water Maze). All of these studies were of a high quality.

With respect to the treatments that were examined by single studies, large treatment benefits were found for motor function (Bilateral Tactile Test) using combined treatment with *magnesium chloride and B2*, or *magnesium chloride*. Neurological and motor function also improved with *CP-98,113, magnesium chloride,* and *dextrorphan* on the Composite Neuroscore, as well as on the Tactile Removal Test using *magnesium chloride*. Treatment with *magnesium sulphate* markedly improved behaviour (Open Field Test), while *CP-98,113*, *HU-211*, *CP-101,606*, and *CP-101,581*, improved spatial learning and memory (Morris Water Maze). There were no other modulators of amino acid activity (*NPS 1506, ketamine, MDL 26,479, eliprodil, aniracetam*) that improved outcome following experimental TBI in rodents (refer to Appendices).

Growth Factors

There were five small sample studies ($N_{Animals}$ 12 to 36) that examined four growth factors (refer to Appendices, Table 3.Q). Three of these treatments showed large to very large improvements in outcome using a controlled cortical impact, weight drop or lateral fluid percussion model of TBI injury (see Table 6).

Spatial learning and memory (Morris Water Maze) improved when rodents were treated with the cell-growth mediating substance *EPO* (erythropoietin) and *BrdU* combined, and in one of the two studies that examined the nerve growth factor *NGF*, while treatment with *EPO* alone improved both recognition memory (Object Recognition) and motor performance (NSS) in mice. There were no improvements in cognition or motor function using the anti-nogo-A monoclonal antibody *mAB 7B12* (see Appendices, Table 3.Q).

Table 6: Weighted mean effect sizes for modulators of amino acid activity, growth factors, and other agents with large treatment effects.

Drug and Measure	Outcome	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
MODULATORS OF AMINO ACID ACTIVITY														
MgSO														
Rotarod	Motor	**2**	14	**30**	severe	WD	**1.81**	.69	**.56**	**3.37**	17	23	high	Heath & Vink, 1998b, 1999
Open Field Test	Behaviour	1	32	30	not specified	WD	1.14		.35	1.93	5	41	moderate	Fromm, Heath et al, 2004
HU-211														
NSS	Motor	**2**	16	**240-360**	not specified	WD	**1.60**	.75	**.44**	**2.92**	15	27	high	Shohami, Novikov et al, 1995
Morris Water Maze	Cognitive	1	22	60	not specified	WD	1.53		.51	2.56	7	29	high	Shohami, Novikov et al, 1995
DCS														
Morris Water Maze	Cognitive	**2**	17	**1,440**	moderate	Lateral FPI	**1.03**	.86	**.06**	**2.29**	9	45	high	Temple & Hamm, 1996
MgCl + B2														
Bilateral Tactile Test	Motor	1	12	60	not specified	CCI	15.64		7.99	23.29	77	2	moderate	Barbre & Hoane, 2006
CP-98,113														
Morris Water Maze	Cognitive	1	23	15	moderate	Lateral FPI	1.66		.63	2.69	7	25	high	Okiyama, Smith et al, 1998
Composite Neuroscore	Motor	1	22	15	moderate	Lateral FPI	.94		.03	1.85	4	45	high	Okiyama, Smith et al, 1998

Cont'd

Table 6 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
MgCl														
Bilateral Tactile Test	Motor	1	12	60	not specified	CCI	1.43		.10	2.76	6	32	moderate	Barbre & Hoane, 2006
Composite Neuroscore	Motor	1	28	60	moderate	Lateral FPI	1.34		.46	2.21	6	35	high	Bareyre, Saatman et al, 1999
Tactile Removal Test	Motor	1	20	15	not specified	CCI	1.03		.06	2.00	4	41	moderate	Hoane, 2005
Dextrorphan														
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.20		.25	2.15	5	38	high	Faden, 1993
CP-101,606														
Morris Water Maze	Cognitive	1	24	15	moderate	Lateral FPI	1.07		.17	1.96	4	41	high	Okiyama, Smith et al, 1997
CP-101,581														
Morris Water Maze	Cognitive	1	25	15	moderate	Lateral FPI	1.04		.17	1.91	4	45	high	Okiyama, Smith et al, 1997
GROWTH FACTORS														
EPO +BrdU														
Morris Water Maze	Cognitive	1	12	1,440	not specified	CCI	2.38		.77	3.99	11	13	high	Lu, Mahmood et al, 2005
EPO														
Object Recognition*	Cognitive	1	36	60	not specified	WD	1.41		.60	2.22	6	32	high	Yatsiv, Grigoriadis et al, 2005

Cont'd

Table 6 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
NSS*	Motor	1	36	60	not specified	WD	.97		.25	1.69	4	45	high	Yatsiv, Grigoriadis et al, 2005
NGF														
Morris Water Maze	Cognitive	1	24	1,440	moderate	Lateral FPI	1.07		.18	1.96	4	41	high	Sinson, Perri et al, 1997
OTHER														
GTSs														
Rotarod	Motor	**2**	12	**5**	not specified	CCI	**-1.91**	1.36	**-3.88**	**-.66**	18	21	high	Ji, Kim et al, 2005
Fenofibrate														
Global Neuroscore	Motor	**2**	14	**360**	moderate	Lateral FPI	**1.50**	.18	**.22**	**2.82**	14	29	high	Besson, Chen et al, 2005
Pyracetum														
Elevated Plus Maze	Behaviour	1	20	not specified	moderate	CCI	8.41		4.93	11.90	41	2	moderate	Zarubina, 2003
Exploratory Activity	Behaviour	1	20	not specified	moderate	CCI	1.83		.69	2.98	8	23	moderate	Zarubina, 2003
Spontaneous Motor Activity	Behaviour	1	20	not specified	moderate	CCI	1.07		.09	2.04	4	41	moderate	Zarubina, 2003
FDP + DMSO														
Grip Test*	Motor	1	16	5	moderate	WD	4.78		2.47	7.08	23	2	high	De la Torre, 1995

Cont'd

Table 6 Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs Lower	95% CIs Upper	Nfs	OL%	Study Quality	Study Reference
NIM811														
Composite Neuroscore*	Motor	1	24	15	severe	CCI	3.85		2.21	5.49	18	3	high	Mybe, Singh et al, 2009
FTS														
NSS*	Motor	1	20	60	moderate	WD	2.28		1.01	3.55	10	16	high	Shohami, Yatsiv et al, 2003
HSA														
Composite Neuroscore	Motor	1	17	15	not specified	Lateral FPI	1.47		.33	2.61	6	29	high	Belayev, Alonso et al, 1999
INO-1001														
Morris Water Maze*	Cognitive	1	22	5	moderate	CCI	.93		.02	1.84	4	48	high	Clark, Vagni et al, 2007

Note: WD = Weight drop injury; CCI = controlled cortical impact injury; Central FPI = central fluid percussion injury; Latera1 FPI = lateral fluid percussion injury ; NSS = Neurological Severity Score

Note: Large treatment effects $N_{studies}$ >1 are presented in bold print

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI

Other

A total of 42 studies used either the weight drop, controlled cortical impact, or lateral fluid percussion model of experimental TBI to examine the effects of 17 treatments that do not fall into any of the above-mentioned groups (see Table 3.R of the Appendices). Three treatments that were examined by multiple high quality studies and six that were examined by single studies of moderate to high quality were associated with large treatment effects (refer to Table 6).

A marked and significant decline in fine motor co-ordination (Rotarod) was found by two studies that investigated the vitanutrient *GTSs* (ginseng total saponin) (see Table 6). Another two studies found that neurological and sensorimotor function (Global Neuroscore) improved with the PPARa agonist *fenofibrate* and one high quality study showed that functional status and motor ability (NSS) in mice benefited from treatment with the ras protein inhibitor *FTS*. In addition, large treatment benefits for behaviour (Elevated Plus Maze, Exploratory Activity, Spontaneous Motor Activity) were evident in a study of adequate quality that administered the ion channel modulator (calcium, potassium, sodium) *pyracetum* to rodents. Moreover, motor function as measured by the Grip Test improved in one study that used mice for combined treatment with *FDP* (glycolytic intermediate) and *DMSO* (free radical scavenger), as well as on the Composite Neuroscore in single studies that administered *NIM811* (cyclophilin inhibitor) to mice or *HSA* (antioxidant) to rats. One further high quality study showed a marked improvement in memory and learning (Morris Water Maze) after mice were treated with the PARP-1 inhibitor *INO-1001*. There were no treatment benefits found for the single studies that examined the neurotrophic *sAPPalpha*, *FDP* alone, or the thromboxane synthetase inhibitor *OKY-046*. Nor were treatment benefits found for the multiple studies that investigated the cannabinoid *2-AG*, the energy substrate *lactate*, the

anionic channel blocker *nizofenone*, anticonvulsant *levetiracetam*, the anti-apoptotic *NBP*, or the phosphodiesterase type 1 inhibitor *VA-045* (refer to Appendices, Table 3.R).

Moderator variables

A range of methodological variables may have influenced these findings (e.g., drug dosage, injury-to-treatment interval, model of experimental TBI, injury severity, rodent type [rat, mouse] or strain). While it was originally intended that these moderator variables would be examined to determine whether they had an impact on the current findings, there were too few studies that investigated the same treatment using the same outcome measure to allow an evaluation of the impact of these variables on treatment effects.

Discussion

This meta-analysis examined data for 5,988 male rodents from 223 experiments that investigated the cognitive, behavioural and motor effects of 91 pharmacological treatments. For current purposes, a treatment was considered to be effective in reducing the cognitive, behavioural or motor problems in rodents after a TBI if there were large and significant improvements in outcome ($d \geq .8$, 95% CIs $\neq 0$), preferably based on multiple high quality studies ($N_{Studies} > 1$), while also taking into account the tendency for journals to publish studies with significant findings ($N_{fs} \geq 3$). When these criteria were applied, there were 16 treatments that improved cognitive and motor outcome (refer to Table 7 for a summary). Behaviour, in general, did not improve with any of the treatments.

Cognition

Of the 16 treatments, six led to improvements in spatial learning and memory, as measured by the Morris Water Maze; namely, *simvastatin*, *atorvastatin*, *C1-INH*, *SNX-185*, *LU 25-109-T*, and *DCS* (see Table 7). *Simvastatin* and *atorvastatin* are HMG-COA reductase inhibitors that

Table 6: Summary of treatments with large beneficial effects ($N_{Studies} > 1$, $N_{fs} > 3$).

Drug and Measure	$N_{Studies}$	Drug Dosage	Measure	M d_w
COGNITION				
Anti-inflammatories				
Simvastatin	2	1mg/kg	Morris Water Maze	2.49
Atorvastatin	3	1mg/kg	Morris Water Maze	1.55
C1-INH*	2	15U	Morris Water Maze	.91
Modulators of Calcium Homeostasis				
SNX-185	3	50 – 200pmol	Morris Water Maze	2.17
Cholinergic				
LU 25-109-T	2	3.6 – 15 umol/kg	Morris Water Maze	1.27
Modulators of Amino Acid Activity				
DCS	2	10 – 30mg/kg	Morris Water Maze	1.03
MOTOR				
Anti-inflammatories				
B3 (Nicotinamide)	2	50mg/kg	Forelimb Placing Test	4.09
C1-INH*	2	15U	Composite Neuroscore	1.30
Vasodilators				
SB 209670	4	7.5mg/kg – 60mg/kg	Neurological Severity Score	1.94
SB 234551	2	15mg/kg – 60mg/kg	Neurological Severity Score	1.56
Modulators of Amino Acid Activity				
MgSO	2	100 – 750umol	Rotarod	1.81
HU-211	2	5mg/kg	Neurological Severity Score	1.60
Modulators of Free Radical Formation				
CDP-Choline	3	100 – 300mg/kg	Composite Neuroscore	1.76
1400W	2	20mg/kg	Global Neuroscore	.98
Other				
Fenofibrate	2	50 – 100mg/kg	Global Neuroscore	1.50
Cholinergic				
ENA 713*	2	1 – 2mg/kg	Neurological Severity Score	1.07

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI

are known to not only minimise vascular damage, inflammation and cell death (apoptosis) following TBI but they are also thought to have regenerative effects that include encouraging the formation of new synaptic connections and the growth of new blood vessels (Lu, et al., 2004; Lu, et al., 2007). Thus, early treatment with these statins may improve the spatial memory of rodents by simultaneously minimising secondary damage and promoting neural restoration. In addition, the C1 esterase inhibitor, *C1-INH* improved spatial memory and learning in mice after a controlled cortical impact injury. Although memory was improved at two different treatment intervals (10 minutes, 1 hour), a large and significant benefit was only found when rodents were treated ten minutes after injury (d = 1.40), suggesting that the efficacy of this agent is time-dependent. *C1-INH* acts to minimise the early activation of immune response systems that can lead to inflammation, free radical production, and poorer outcome (Longhi, et al., 2009).

The single N-type voltage-gated calcium channel blocker, *SNX-185*, also resulted in large improvements to spatial learning and memory at three different dosages (50pmol [picomoles] d = 1.27; 100pmol d = 3.61; 200pmol d = 2.94). This drug acts to block the over-activation of N-type calcium channels, thereby minimising the impact of excitotoxicity and oxidative stress that has been implicated in secondary cell death after TBI (Lee, et al., 2004).

There was also a single cholinergic agent and partial muscarinic M1 agonist and M2 antagonist, *LU 25-109-T* that improved spatial learning and memory when treatment was administered to rats 24 hours after a moderate central fluid percussion injury. While this drug improved memory at two different dosages (15umol [micromole], and 3.5umol), the higher dose resulted in a larger and significant improvement (d = 1.98), suggesting that the benefits are dose-dependent. It is thought that this treatment may improve cognition by stimulating the release of acetylcholine in the brain, which plays a vital role in memory and learning (Pike & Hamm, 1997).

Finally, rats that were treated with the modulator of amino acid activity and partial agonist of the NMDA receptor *DCS* (D-cycloserine) 24 hours after a moderate lateral fluid percussion injury performed better on a memory task. While an initial increase in glutamate following TBI has been linked to excitotoxicity and neuronal death (Yaka, et al., 2007), prolonged reductions in the availability of glucose in the hours after the initial injury have been linked to the subsequent development of cognitive problems in rodents (Hamm, Temple, Pike, & Ellis, 1996). The data from this study suggests that when glutamate release is increased in rodents one day after a TBI, cognition improves. Moreover, more marked improvements occur at the higher 30mg/kg dose (d = 1.78) compared to a lower dose of 10mg/kg (d = .57), again suggesting that there are dose-dependent treatment effects.

Motor function

With respect to motor function, there were ten treatments that were efficacious ($d \geq .8$, $N_{Studies} > 1$, large N_{fs}, 95%CIs > 0), including two anti-inflammatories (*B3*, *C1-INH*), two vasodilators (*SB 209670*, *SB 234551*), two modulators of amino acid activity (*magnesium sulphate*, *HU-211*), two modulators of free radical formation (*CDP-choline*, *1400W*), the PPARa agonist *fenofibrate*, and the acetylcholinesterase inhibitor *ENA 713* (see Table 7).

Of the anti-inflammatories, the vitanutrient *B3* administered at a dose of 50mg/kg, resulted in large improvements to sensorimotor function (Forelimb Placing Test). The biochemical effects of B3 are thought to arise from reducing the effects of ATP depletion and oxidative stress, which can lead to secondary neural damage and, consequently, cognitive, behavioural and/or motor impairments after TBI (Hoane, Akstulewicz, & Toppen, 2003; Hoane, Tan, Pierce, Anderson, & Smith, 2006). In addition, a dose of 15U (units) of the C1 esterase inhibitor *C1-INH* showed large and significant benefits to sensorimotor function (Composite Neuroscore) when treatment was administered at both ten minutes (d = 1.63) and one hour (d = 1.03) after injury, suggesting that these improvements were not time-dependent.

Large improvements in functional status (balance, alertness, reflexes) and motor function were also found for two vasodilators, *SB 209670*, and *SB 234551*, as measured by the Neurological Severity Score. SB 209670 and SB 234551 are selective antagonists of the endothelin-A-receptor and act to minimise vasoconstriction and, consequently, a reduction in blood flow that can increase ischemic injury (Barone, et al., 2000). In addition, these treatments were examined at different dosages; four dosages for SB 209670 and two dosages for SB 234551. Large benefits were found for SB 209670 when it was administered at the moderate [15mg/kg (d = 4.69) and 30mg/kg (d = 4.08)] and highest dose of 60mg/kg (d = 2.31) but not at the lowest dose of 7.5mg/kg (d = .59). Furthermore, large improvements were also found for SB 234551 at the moderate [15mg/kg (d = 1.06)] and higher [60mg/kg (d = 2.43)] dosages, suggesting that these drugs have dose-dependent treatment effects in rodents.

The inhibitor of glutamate release, *magnesium sulphate*, on the other hand improved fine motor co-ordination (Rotarod) within thirty minutes of a weight drop injury. Two dosages of magnesium sulphate showed large treatment benefits (750umol [micromole] d = 2.26, and 100umol d = 1.48). Magnesium sulphate acts as an NMDA antagonist and inhibitor of glutamate release, thereby minimising excitotoxic damage to the brain which is itself associated with poorer outcome following TBI (Browne, Leoni, Iwata, Chen, & Smith, 2004; Fromm, et al., 2004; Hoane, Knotts, Akstulewicz, Aquilano, & Means, 2003). Moreover, magnesium plays a vital role in a number of cellular processes that may be disrupted following TBI and are critical to cell survival, such as cellular respiration, glycolysis, and oxidative phosphorylation (Heath & Vink, 1998a, 1998b). Furthermore, *HU-211* (dexanabinol) is a non-competitive NMDA receptor antagonist which, when administered at a dose of 5mg/kg results in improvements to functional status and motor performance, as measured by the Neurological Severity Score. The efficacy of this agent was not time-

dependent, with large and significant benefits found for rodents treated at both four (d = 2.21) and six hours (d = 1.15) after injury. This treatment acts to prevent cellular toxicity, which results from a calcium influx via NMDA receptors, and decreases cytokines in the brain, which are implicated in inflammation, increased intracranial pressure and poorer outcome following TBI (Belayev, Busto, Zhao, & Ginsberg, 1995; Knoller, et al., 2002).

In addition, two modulators of free radical formation, the phospholipid intermediate *CDP-choline* and the NOS inhibitor *1400W*, improved neurological function and sensorimotor performance in rats on the Composite Neuroscore and the Global Neuroscore, respectively. CDP-choline is thought to reduce membrane damage and oedema formation that can lead to neurological damage and impairment following TBI (Dempsey & Rao, 2003; Dixon, Xiecheng, & Marion, 1997). In addition, CDP-choline results in raised brain concentrations of acetylcholine after TBI, deficiencies of which can cause cognitive and behavioural problems (Dixon, et al., 1997). Although three dosages of this drug were administered, treatment benefits were only found for the moderate (200mg/kg; d = 3.67) and higher (400mg/kg; d = 3.52) dosages, and not at the lowest dose (100mg/kg; d = .65), suggesting that higher dosages of CDP-choline soon after a TBI are necessary to improve outcome. Administration of the NOS inhibitor 1400W at a dose of 20mg/kg between five minutes and six hours after a lateral fluid percussion injury of unspecified severity also improved sensorimotor activity (Global Neuroscore), although a large and significant effect was only found at the earlier (5 minutes; d = 1.33) but not the later (6 hours; d = .74) treatment interval, suggesting that these improvements are time-dependent. Overactivation of NOS (nitric oxide synthase) has been implicated in cell death and vascular damage following TBI (Silver, McAllister, & Yudofsky, 2005; Webster, 2003). Thus, 1400W may exert a neuroprotective effect by interrupting early secondary injury processes after TBI.

Finally, treatment with the PPARa agonist *fenofibrate* six hours after a moderate lateral fluid percussion injury improved sensorimotor outcome, as measured by the Global Neuroscore, while the acetylcholinesterase inhibitor *ENA 713* improved alertness and motor outcome (Neurological Severity Score). The PPARa (peroxisome proliferator-activated receptor a) agonist fenofibrate plays a role in the regulation of lipid, protein, carbohydrate and glucose metabolism, which is often disrupted following TBI, resulting in inflammation, excitotoxity, cell death and poorer outcome (Besson, Chen, Plotkine, & Marchand-Verrecchia, 2005). Two different dosages of this treatment were administered, with large benefits found for both [50mg/kg (d = 1.65) and 100mg/kg (d = 1.40)]. Although treatment with the acetylcholinesterase inhibitor ENA 713 improved alertness and motor function after severe TBI, a large and significant benefit was only found at the higher [2mg/kg (d = 3.46)] but not the lower [1mg/kg (d = .07) dosage. ENA 713 is a brain-selective acetylcholinesterase inhibitor that acts to increase brain concentrations of acetylcholine, and has been found to reduce blood-brain barrier disruptions, oedema formation and resultant neuronal loss in both rats and mice following TBI, thereby reducing motor impairments after injury (Chen, Shohami, Bass, 1998; Chen, Shohami, Constantini, et al., 1998).

Other beneficial treatments requiring further investigation

There were a large number of other treatments that additionally showed large benefits to cognition, behaviour and motor function in rodents following TBI but were only investigated by one study. These include catecholaminergic treatments (rasagiline, methylphenidate, L-deprenyl), modulators of ion homeostasis (ziconotide), TRH analogues (TRH 35b, YM 14673, YM 14673 + nalmefene, 2-ARA-53a), opioids (nalmefene + dextrorphan), anti-inflammatories (IL-18BP, VCP), immunosuppressants (cyclosporin A), modulators of free radical formation (bemithyl, DETA/NONOate, PBN, B2, DMSO, Murine IgG, Anti-ICAM, L-NIL, Inosine), steroids (raloxifene), modulators of amino acid activity

(MgCL + B2, FDP + DMSO, CP-98,113, MgCl, dextrorphan, CP-101,606, CP-101,581), growth factors (EPO + BrdU, EPO, NGF) and others (pyracetum. INO-1001, NIM811, HSA, FTS). Further evaluations of these treatments are needed to verify these findings before they are trialled in clinical studies.

Limitations of the Current Findings

There are several limitations to the current study. Firstly, the exclusion of non-English studies reduced the number of studies that were eligible for analysis. Secondly, there were large numbers of studies that failed to report, or provide upon written request, data that could be converted into an effect size (e.g., data were presented in figures, precluding the extraction of exact data). Every endeavour was made to contact these authors. This highlights the need for authors to routinely report exact means and standard deviations in their results.

Thirdly, injury severity was measured in terms of the force of TBI impact. However, a variety of different metrics were used (e.g., pressure, weight, velocity), with only 110 of the 214 studies specifying the degree of severity (e.g., mild, moderate, or severe). The results of different studies could be more accurately compared if injury severity was reported in a consistent manner. Similarly, drug dosages were often measured using different metrics (i.e. mg/kg, picomole), making it difficult to combine or compare the findings from different studies; indicating a need for uniformity in how dosages are reported.

Fourthly, the current findings may be affected by the selective inclusion of studies that examined only male rodents. While intact male and female animals should be examined prior to their investigation in a clinical population, the small number of studies that examined intact females, combined with the potential for sex differences in outcome (O'Connor, Cernak, & Vink, 2003), meant that their inclusion may have muddied the results. Additionally, rats and mice may differ in their biochemical response to injury (Ji, Kopin, & Logsdon, 2000; Brauze,

Januchowski, & Szyfter, 2002) and this may play an important role in outcome after TBI. However, there were too few studies that examined both using the same treatment and study protocol to evaluate the influence of rodent type on treatment efficacy.

Finally, an important precursor to undertaking both experimental and clinical research is to ensure that a study has sufficient power to detect a significant treatment effect where one exists. Few studies reported undertaking power analyses and many used small samples, raising the possibility that some studies were underpowered. By combining data from a number of studies, a meta-analysis increases the power to detect significant treatment effects and, therefore, the veracity of the findings.

Conclusions

A wide range of treatments have been evaluated in rodents to determine their efficacy in reducing the cognitive, behavioural and motor problems that are caused by TBI. Of these, six treatments improved cognition and ten improved motor function. There were no treatments, which met the study criteria, that improved behaviour. Spatial learning and memory, as measured on the Morris Water Maze, was improved with three anti-inflammatories (simvastatin, atorvastatin, C1-INH), one calcium channel blocker (SNX-185), one cholinergic agent (LU 25-109-T), and one modulator of amino acid activity (DCS). Functional status and motor function, on the other hand, showed improvement on one of five outcome measures (Forelimb Placing Test, Rotarod, Composite Neuroscore, Global Neuroscore, Neurological Severity Score) after treatment with two anti-inflammatories (B3, C1-INH), two vasodilators (SB 209670, SB 234551), two modulators of amino acid activity (magnesium sulphate, HU-211), two modulators of free radical formation (CDP-choline, 1400W), the PPARa agonist fenofibrate and the cholinergic agent ENA 713. Moreover, five of these showed dose-dependent treatment effects (LU 25-109-T, DCS, CDP-choline, ENA 713, and SB 209670), and were either not effective or less effective at the lowest dosages,

emphasising the importance of investigating a range of dosages. In addition, two treatments showed treatment interval effects (1400W and C1-INH), with marked benefits to motor function and cognition only evident when rodents were treated within the first ten minutes of injury. This highlights the need to examine a variety of different injury-to-treatment intervals in order to identify the optimal time for treatment. Although these findings indicate that treatment benefits can be found across a range of models of TBI injury (controlled cortical impact, lateral fluid percussion, central fluid percussion, weight drop), the majority of studies (70%) used a focal model of TBI (controlled cortical impact or weight drop). Moreover, large treatment effects occurred more frequently when treatment was administered very early ($\leq$ 1 hour post-injury). In contrast, human TBI involves both focal and diffuse brain injuries, with treatment generally initiated beyond one hour post-injury. These factors may impact on the extent to which this experimental research translates to a clinical population and suggests that a variety of models of TBI injury (focal and diffuse) and both early and late treatment intervals should be examined before investigating treatment efficacy in clinical settings. Finally, although none of the studies that were included in this meta-analysis evaluated drug concentrations in the target brain regions, it can probably be assumed that significant treatment effects indicate that local drug concentrations were adequate. This assumption may not apply to non-significant or negative findings.

Recommendations

Based on the findings of this study, there are a number of recommendations that can be made. Firstly, while a range of measures were used to evaluate treatment efficacy in rodents, the Morris Water Maze (cognition), the Composite Neuroscore, and the Neurological Severity Score (motor function) were used most frequently. Large and significant treatment effects were more likely when these measures were used to assess outcome, suggesting that

they may be more sensitive to functional improvements and the best options for evaluating efficacy. Secondly, of the treatments that met the current criteria for efficacy, anti-inflammatories showed the largest benefits; however anti-inflammatories, cholinergic agents and modulators of amino acid activity all improved both cognition and motor function. Finally, the different chemical groups have not received equal research attention, which is evident in the distribution of studies analysed here. Of the chemical groups that were examined most frequently, anti-inflammatories and modulators of free radical formation were the most efficacious, although in the latter case these benefits may be dependent on severity of injury (e.g., only evident with ischemia/reperfusion). In contrast, modulators of amino acid activity were the least likely to improve outcome, as reflected in the larger number of negative trials. While the findings from this study are promising, it is necessary to separately evaluate whether these treatment benefits translate to a human TBI population.

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P. Wheaton and J. Mathias report no conflicts of interest. While R. Vink has published research in this area, this author was not involved in the literature searches, study selection, or data extraction or analysis. Rather, R Vink provided expertise in animal models of TBI, the classification of treatments and their modes of action, and the interpretation of the study findings.

The analysis and conclusions reported in this paper are entirely those of the authors and do not reflect those of the Editors of the Journal of Psychopharmacology, the British Association for Psychopharmacology, or Sage Publications.

Appendices

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Chapter 4 : Impact of early pharmacological treatment on cognitive and behavioural outcome after traumatic brain injury in adults: A meta-analysis

The previous study found that a range of treatments improved cognition and motor function when administered to rodents soon after a TBI. Of these, anti-inflammatories were particularly efficacious in reducing cognitive and motor problems. However, it is unclear whether early treatment with a pharmacological agent also benefits outcome in humans who have sustained a TBI. Therefore, a second meta-analysis was conducted to evaluate the efficacy of early treatment with a pharmacological agent on cognitive and behavioural outcome in adults following TBI.

A number of differences exist between the preceding animal study (Chapter 3) and the following two clinical studies (Chapters 4 and 5). Firstly, although a large number of different treatments were examined in the animal literature, only a small number of these have been investigated in clinical research. Therefore, a higher standard of treatment efficacy; namely a large treatment effect ($d \geq .8$), was set for the previous study and a moderate effect for the clinical studies ($d \geq .5$), because of the limited application of experimental research to a human TBI population.

Secondly, when the first paper was accepted for publication, the Journal Editor requested a different method for categorising the drugs. Unfortunately, the manuscript for the second study had already been accepted for publication, therefore it was not possible to alter the classification system used in the second and third studies to make it consistent with the previous study. While this impacts on the categorisation of treatments, it does not alter the results in any way.

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TITLE: Impact of early pharmacological treatment on cognitive and behavioural outcome after traumatic brain injury in adults: A meta-analysis.

AUTHORS: P Wheaton, J L Mathias, R Vink

Abstract

Early pharmacological treatments have the potential to reduce some of the disabling cognitive and behavioural problems that result from traumatic brain injury (TBI). Although a large number of treatments have been developed, clinical research has yielded inconsistent findings with respect to the effectiveness of these pharmacological treatments on cognitive and behavioural outcome. Furthermore, their relative efficacy has not been evaluated, thereby hindering advances in the treatment of TBI. A meta-analysis of research that examined the impact of early pharmacological treatments on cognitive and behavioural outcome following TBI between January 1980 and May 2008 was, therefore, undertaken. The PubMed and PsycInfo databases were searched using 35 terms. All articles were screened using detailed inclusion criteria. Weighted Cohen's *d* effect sizes, percent overlap statistics and Fail safe N statistics were calculated for each pharmacological agent. Studies that used different experimental designs were examined separately. 11 pharmacological treatments were investigated by 22 clinical studies, comprising 6,472 TBI patients in the treatment groups and 6,460 TBI controls. One dopamine agonist (amantadine) and one bradykinin antagonist (CP-0127, Bradycor) produced marked treatment benefits ($d \geq .8$) for a single measure of arousal (GCS). Notably, drug dosage and the measure chosen to assess outcome influenced the probability of finding a treatment benefit.

Keywords: early, pharmacological treatment, traumatic brain injury, meta-analysis, adults

Introduction

Traumatic brain injury (TBI) is the leading cause of preventable death, as well as physical and neuropsychological impairment, in people under the age of 45 years (Elovic & Zafonte, 2005; Engel, Slemmer, Vlug, Maas & Weber, 2005; Javouhey, Guerin, & Chiron, 2006; Lee, Lyketsos, & Rao, 2003). TBI is defined as a sudden and forceful impact to the head that disrupts the neurological and neurochemical function of the brain (Elovic & Zafonte, 2005; Engel, et al. 2005). A variety of neurochemical changes occur in the early stages after injury (Royo, Shimizu, Schouten, Stover, & McIntosh, 2003), including the excessive activation of glutamate receptors (excitotoxicity), the over-production of toxic levels of oxidants (free radical generation), the accumulation of intracellular calcium (disruptions to ion homeostasis), as well as inflammatory processes (Cooper, Bloom, & Roth, 2003; Novack, Dillon, & Jackson, 1996; Webster, 2003), which are associated with the subsequent development of neurological deficits. Acutely administered pharmacological treatments may play a neuroprotective role in the treatment of TBI by interrupting these early biochemical disruptions in the brain, potentially reducing the severity of an injury and the degree of cognitive and behavioural impairment sustained by survivors (Cawley, Marburger, & Earl, 1998; Dieli, 2002; Guha, 2004; Mendez, Corbett, Macias, & Laptook, 2005; Royo, et al., 2003; Shimuzu, Fulp, Royo, & McIntosh, 2005; Viano, von Holst, & Gordon, 1997). While there is no accepted time frame for these acute neurochemical changes, they are generally thought to occur in the hours to days after an injury (Faden, 2001).

Although pharmacological treatments that target these acute neurochemical events have been shown to reduce neuronal damage and improve cognitive and behavioural outcome in rodent models of TBI (Aoyama, et al., 2002; Berman, Verweij, & Muizelaar, 2000; Clifton, et al., 1989; Kaplanski, et al., 2002; Lee, Galo, Lyeth, Muizelaar, & Berman, 2004; Panikashvili, et al., 2001; Smith, Okiyama, Gennarelli, & McIntosh, 1993; Smith, Okiyama,

Thomas, & McIntosh, 1993), clinical trials in the human TBI population have shown mixed results (Faden, 2001; Narayan, Michel, & Group, 2002). For example, patients treated acutely with *glutamate antagonists* following TBI have shown improved outcome in some cases (tradoprodil, gacyclidine, propofol, selfotel) (Kelly, et al., 1999; Lepeintre, et al., 2004; Stewart, Bullock, Teasdale, & Wagstaff, 1999; Yurkewicz, Weaver, Bullock, & Marshall, 2005), but not in others (selfotel, valproate, magnesium) (Dikmen, Machamer, Winn, Anderson, & Temkin, 2000; Morris, et al., 1999; Temkin, et al., 2007), while those treated with *free radical scavengers* (pergorgotein, tirilazad mesylate) have shown improvements in survival and global outcome (Marshall, et al., 1998; Muizelaar, et al., 1993; Young, et al., 1996), which may be dose-dependent (pergorgotein) (Young, et al. 1996) or specific to patients with subarachnoid haemorrhage (tirilazad mesylate) (Marshall, et al. 1998). Acute treatment with the *calcium channel blocker* nimodipine (Bailey, et al., 1992; Bailey, et al., 1991; The European Study Group on Nimodipine in Severe Head Injury, 1994), as well as *sodium channel blockers* (carbamazepine, lamotrigine) (Azouvi, et al., 1999; Chahine & Chemali, 2006; Chatham-Showalter, 1996; Chatham-Showalter & Netsky Kimmel, 2000), has also improved global outcome, although contradictory findings have been reported (nimodipine) (Pillai, Kolluri, Mohanty, & Chandramouli, 2003). With respect to *anti-inflammatory* agents, a favourable outcome has been reported with some steroids following TBI (triamcinolone, combined treatment with dexamethasone, barbiturates and hyperventilation) (Grumme, et al., 1995; Hoppe, Christensen, & Christensen, 1981), but not with others (dexamethasone alone, methylprednisolone, tromethamine) (Braakman, Schouten, Blaauw-van Dishoeck, & Minderhoud, 1983; CRASH Trial Collaborators, 2005; Dearden, Gibson, McDowall, Gibson, & Cameron, 1986; Gaab, et al., 1994; Giannotta, Weiss, Apuzzo, & Martin, 1984; Saul, Ducker, Salcman, & Carro, 1981; Wolf, et al., 1993). Additionally, while the *central nervous system stimulant* methylphenidate improved cognition and

behaviour following TBI (Gualtieri & Evans, 1988), benzodiazepines, narcotics and neuroleptics did not (Napolitano, Elovic, & Qureshi, 2005). Alternatively, *serotonin agonists* (repinotan, combined treatment with dihydroergotamine and metoclopramide) (McBeath & Nanda, 1994; Ohman, Braakman, & Legout, 2001), the *cannabinoid* dexanabinol (Knoller, et al., 2002), and *peptides* (cerebrolysin, anatibant, bradycor, desmopressin) (Filipova, Jung, & Krejcova, 1989; Marmarou, et al., 2005; Marmarou, et al., 1999; Narotam, et al., 1998; Wong, Zhu, & Poon, 2005), have shown small improvements to global outcome following TBI, although contradictory findings have also been reported (dexanabinol and vasopressin) (Bohnen, Twijnstra, & Jolles, 1993; Maas, et al., 2006).

Importantly, these studies have used different methodologies with respect to the participants' age, severity of injury, post-injury treatment interval, drug dosage and experimental design (i.e., independent groups repeated measures and independent groups designs, including randomised clinical trials). These differences may contribute to the discrepant findings (Filipova, et al., 1989; Lepeintre, et al., 2004; Silver, McAllister, & Yudofsky, 2005). Moreover, variability between studies with respect to the number of participants recruited may also impact on the likelihood of finding a significant treatment effect, with a statistically significant change more likely to be detected in larger samples (Tilley, 1996). Finally, cognitive and behavioural outcome has been evaluated with a variety of different tests (e.g., Glasgow Outcome Scale, Glasgow Coma Scale, various cognitive tests) that use different scales of measurement (i.e. continuous, discrete) and may be differentially sensitivity to treatment effects (Satz, et al., 1998), making it difficult to directly compare findings (Tilley, 1996).

A meta-analysis provides an objective and quantitative means by which to standardise the research data, thereby enabling direct comparisons between different treatments and the formulation of evidence-based treatment recommendations. To this end, the current study

undertook a systematic review and meta-analysis of existing research that has evaluated the impact of acutely administered (≤ 7 days post-injury) pharmacological treatments on cognitive and behavioural outcome following TBI.

Methods

Search Strategy and Selection Criteria

A comprehensive search was undertaken of the PsychINFO and PubMed electronic databases from January 1980 to May 2008 in order to identify published articles that examined the impact of acute pharmacological treatments on cognitive and behavioural outcome following a TBI. The 35 search terms were deliberately kept broad in order to capture all relevant articles (refer to Table 4.A of the Appendices). In addition, the bibliographies of all studies that were retrieved were examined to identify any relevant research.

For a study to be included in the current meta-analysis, it had to meet the following inclusion criteria: (a) was published in a journal; (b) was published in English; (c) included a TBI control group that was matched to the treatment group on the basis of age and injury severity; (d) was not a case study; (e) had a TBI treatment and TBI control group that had sustained non-penetrating TBIs; (f) both groups were administered measures of cognition and/or behaviour to assess outcome (i.e. studies using only electrophysiological measures were excluded); (g) the treatment group was administered a pharmacological agent in the acute stages after injury (≤ 7 days post-injury); (h) no participant was known to have: sustained a TBI prior to the current injury, had any pre-existing motor, visual, language or learning impairments, a documented history of psychiatric illness or substance abuse, or recently been treated with another pharmacological agent that was designed to enhance

cognition or behaviour; (i) the results were reported in a format that enabled the calculation of an effect size (i.e., means, standard deviations, *t* tests, *F* ratios from a one-way analysis of variance, exact *p* values) or authors provided this information in response to a written request; and (j) participants were aged 16 years or older. Where age ranges for the treatment or control groups were not reported, a study was deemed eligible if the mean age +/- one standard deviation met these criteria.

The literature searches identified 10,822 potentially relevant articles (refer to Figure 4.1 of the Appendices). A preliminary application of the inclusion criteria to the titles and abstracts of these studies identified a total of 40 studies that were relevant to the current meta-analysis. Full-text versions of these papers were then retrieved. Application of the inclusion criteria to the full-text versions of these studies revealed that 25 did not meet one or more of the inclusion criteria, leaving 15 studies. An examination of the bibliographies of all retrieved articles did not identify any other studies. Upon written request, the corresponding author of one study (Bohnen et al., 1993) provided additional data that enabled this study to be included in the current meta-analysis.

Treatment effects may be influenced by drug dosage which, if averaged, may conceal differential effects. If a study administered different dosages of a drug to separate treatment groups and compared them to the same control group, these data were analysed separately. On three occasions (Lepeintre, et al., 2004; Muizelaar, et al., 1993; Ohman, et al., 2001), a single study was treated as three separate studies and on one occasion (Marmarou, et al., 2005), a single study was treated as two separate studies because different dosages of a single drug were administered to different treatment groups. Thus, data from a total of 22 studies were analysed. All of the studies involved placebo-control, with the majority also randomised and blinded (e.g., three did not report randomisation; and two did not report blinding). None were open-label studies. A total of 11 different treatments were examined by these studies.

Demographic and bibliographic details for each study, together with the outcome measures that were used, are provided in Table 4.B of the Appendices and a separate reference list for these studies is provided in Appendix 4.A of the Appendices.

Research Designs

Two different research designs were used to examine treatment effects, these being an independent groups repeated measures design and an independent groups design (which includes randomised clinical trials). An *independent groups repeated measures design* involved assessing two groups (Treatment and Control) on two occasions (pre- and post-treatment), with the independent variable being group and the dependent variable being the change in pre-post treatment cognitive or behavioural outcome. An *independent groups design*, on the other hand, involved assessing two groups (Treatment and Control) on only one occasion (post-treatment), with the dependent variable being post treatment cognitive or behavioural outcome. Both research designs minimise the confounding effects of spontaneous recovery and test practice (i.e., improvements to performance arising from test familiarity) because they are assumed to affect both groups equally. However, only the former design controls for group differences in baseline performance, making it a better experimental design for evaluating treatment efficacy. Different formulas are required for the calculation of effect sizes for these research designs, therefore, the results were treated separately (Morris & DeShon, 2002).

Data Preparation

In some cases, outcome was assessed on multiple occasions during or following treatment which, if averaged, may obscure important information. For example, in cases where there are large treatment effects in the early stages of a study and small effects at the end, the average would be larger than for a study where only a final post-treatment score was reported. As not all studies assessed outcome repeatedly, only data from the final session at

the end of, or after completion of, the treatment were used to calculate effect sizes. One exception to this was the Glasgow Outcome Scale (GOS), which is routinely administered at three and/or six months post-injury (Jennett, 2005). Effect sizes were, therefore, calculated for the GOS at both three and six months in order to compare treatment benefits at two times post-injury.

Some basic transformations to standardise the data were necessary before it was analysed. Firstly, standard errors were transformed to standard deviations to enable the calculation of effect sizes. Secondly, the data for a number of descriptive variables were transformed to ensure a common scale of measurement. Thus, post-injury interval and time-to-treatment were expressed in terms of hours. Thirdly, while there is some controversy about calculating means and standard deviations for categorical data (Gaito, 1980; Townsend & Ashby, 1984), it has been argued that it is appropriate to do so where the ranks reflect the patient's level of disability (Wang, Yu, Wang, & Huang, 1999), which is the case with the GOS. Consequently, GOS data that were reported as the number of participants within each category (1 = deceased, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability, 5 = good outcome) were transformed to means and standard deviations to allow for the calculation of effect sizes.

Each treatment that was included in this meta-analysis was categorised into a chemical group, pharmacological category, and primary method of action, the details of which are set out in Table 4.C of the Appendices. This system was adopted to simplify the presentation of data and is not intended to imply that the method of action of these drugs is limited to a single type.

Statistical Analysis

The effect size measure used for the current meta-analysis was Cohen's *d*, which was calculated using the methods set out by Morris and DeShon (2002) for those studies that used

an independent groups repeated measures experimental design and Zakzanis (2001) for those that used an independent groups experimental design. Cohen's *d* is not influenced by sample size and measures the difference between two means divided by the pre-treatment standard deviation, for the independent groups repeated measures experimental design (Morris & DeShon, 2002) (i.e. treatment vs control pre-post treatment change), or the pooled standard deviation, for the independent groups experimental design (Zakzanis, 2001) (i.e. treatment vs controls post-treatment) (Zakzanis, et al., 1999). If means and standard deviations were not provided for a study, *t* values, one-way *F* statistics and exact *p* values were converted to *d* using the formula provided by Zakzanis (2001). Where exact *p* values were reported, the appropriate *t* statistic was derived from a table provided by Lipsey and Wilson (2001) and this measure was used to calculate *d* (Lipsey & Wilson, 2001)

A multi-stage process was used in the calculation of effect sizes for each treatment. The first step involved calculating an effect size for each score for every outcome measure of cognition and behaviour that was used by a study. If a study provided multiple scores for an outcome measure, these were combined and an average effect size for that measure was calculated. The effect sizes obtained from different studies that used the same measure were then averaged to allow an evaluation of the combined findings.

All effect sizes were calculated in such a way that a positive Cohen's *d* indicated that treatment with a specific pharmacological agent improved cognitive and/or behavioural outcome. Cohen (1977, 1992) defines a small effect as $d \geq .2$, a moderate effect as $d \geq .5$, and a large effect as $d \geq .8$. To put this statistic into perspective, an effect size of .5 indicates that there is a difference of one half of a standard deviation between the mean outcomes of the two groups.

The reliability of an effect size is affected by the size of the sample from which it is derived, making it important to weight effect sizes by sample size before they are averaged

(Hunter & Schmidt, 2004; Lipsey & Wilson, 2001; Rothstein, et al., 2005). An overall weighted mean effect size was calculated by weighting each of the effect sizes from individual studies by its sample size and then averaging them. Studies may also vary in terms of their methodological quality. More confidence can be placed in the findings of high quality studies because they control for more variables and provide more information to allow the reliability of the findings to be assessed (Hunter & Schmidt, 2004). All studies were, therefore, additionally weighted by their methodological quality. Two independent raters (P.W. and a trained third year undergraduate student) assessed the methodological quality of each study using a rating scale that was based on the criteria scale used by Sindhu, Carpenter and Seers (1997) (refer to Table 4.D of the Appendices). All studies were rated independently by each rater, after which the scores for each study were reviewed and any anomalies discussed until a consensus rating was achieved. A mean effect size, weighted by study quality, was calculated by weighting the effect sizes for each study by the quality score for that study and then averaging across studies.

A percentage overlap score (%OL) was also calculated to provide a measure of the extent to which the test scores from the two groups overlap. The %OL is inversely related to the magnitude of an effect size and is based on an inversion of idealized population distributions (Zakzanis, et al., 1999). A %OL score was calculated using the table provided by Zakzanis (1999), whereby an effect size of 0.00 is associated with complete overlap (100%), and an effect size of 4.00 is associated with almost complete discrimination between groups (2.3% overlap). Ninety-five percent 95% confidence intervals, which provide a measure of the range and precision of an estimated mean effect size (Hedges & Olkin, 1985; Lipsey & Wilson, 2001), were to be calculated, however, not all studies reported the data that was necessary for this calculation. Instead, minimum and maximum effect sizes are reported. Finally, a common criticism of meta-analytic reviews is that studies with significant findings

are more likely to be published (publication bias) and this may inflate the magnitude of an effect size (Rosenthal, 1995). A fail-safe N (N_{fs}) was, therefore, calculated for each effect size to examine the potential impact of this problem. This statistic provides a measure of the number of unpublished studies, which have found a small treatment effect (i.e. Cohen's $d \leq .2$), that are needed to call the current findings into question (Zakzanis, 2001).

Data Interpretation

Mean Cohen's *d* effect sizes (standard deviation, minimum/maximum), weighted by sample size (d_{wss}) were calculated for each of the cognitive and/or behavioural tests that were used to evaluate the effects of 11 pharmacological treatments. N_{fs} and %OL scores were also calculated and effect sizes were additionally weighted for methodological quality (d_{wsq}). The conclusions drawn from this meta-analysis are based on the combined interpretation of these statistics. It is argued that we would be more confident that a treatment has improved cognitive and/or behavioural outcome if there is a moderate to large difference between groups ($d_w \geq .5$ to $\geq .8$) and if it is unlikely that there would be a sufficient number of unpublished studies to draw the current findings into question (i.e., large N_{fs}). Additionally, given that an independent groups repeated measures design is a more rigorous research design, greater weight was placed on the results of studies that used this design. As new treatments may only have been investigated by a single study, the effect sizes calculated from both multiple studies and single studies were considered.

Findings are presented separately for 8 categories of chemicals (serotonergic, catecholaminergic, calcium channel blockers, NMDA antagonists, steroids, peptides, cannabinoids, free radical scavengers). Cognitive and behavioural outcomes are then reported for each drug within these categories, rank ordered by study design (i.e., independent groups repeated measures followed by independent groups) and effect size (largest to smallest). Those pharmacological treatments that produced sizeable treatment effects ($d \geq .8$) in which

reasonable confidence could be placed (i.e., investigated using an independent groups repeated measures experimental design, a large sample, a large fail safe N (N_{fs}), small %OL) are of greatest interest to this analysis.

Results

Patient Characteristics

The data for 12,932 participants from 22 studies contributed to the current meta-analysis (refer to Table 1), comprising 6,472 TBI patients treated with a pharmacological agent (79% male, 21% female) and 6,460 control patients who were given standard treatment only or a placebo (79% male, 21% female). The majority of studies recruited patients with a severe TBI (N = 19), while the remainder were of mixed (N = 2) or mild (N = 1) injury severity. As Table 1 shows, less than a third of studies (N = 7) reported specific injury severity data (i.e. GCS). No study reported duration of post-traumatic amnesia (PTA), loss of consciousness (LOC) or education level. Additionally, only 15 studies reported the average injury-to-treatment interval for the treatment group. When age, GCS and injury-to-treatment interval were compared for those studies that provided this information, the treatment and control groups did not differ significantly on any of these variables ($t_{(38)}$ = .63, p = .5; $t_{(12)}$ = .01, p = .1; $t_{(18)}$ = .4, p = .5, respectively), suggesting that these groups were well matched. A total of three studies used an independent groups repeated measures experimental design and 19 studies used an independent groups experimental design to assess treatment efficacy.

Table 1: Demographic and injury data for the TBI treatment and placebo control groups

	TBI TREATMENT					TBI CONTROLS				
	$N_{studies}$	**$N_{participants}$**	**M**	**SD**	**Range**	**$N_{studies}$**	**$N_{participants}$**	**M**	**SD**	**Range**
Participants	22	6472	294.2	1059.4	9 - 5007	22	6460	293.6	1058.2	4 - 5001
Age (years)	20	1037	33.8	4.5	27.0 - 42.1	20	1041	32.0	6.2	25.4 - 44.0
GCS	7	226	6.6	2.4	4.5 - 12.0	7	224	6.6	2.5	4.7 - 12.2
Time from injury (hours)	15	935	14.0	22.0	2.0 - 72.0	10	660	10.0	11.0	3.5 - 40.0

Note: $N_{participants}$ = total number of participants contributing to M = mean, SD = standard deviation and Range; $N_{studies}$= total number of studies contributing to M = mean, SD = standard deviation and Range; GCS = Glasgow Coma Scale.

Serotonergic Treatments

There were three studies that investigated the treatment of TBI with the serotonin agonist *BAY X 3702*, also known as repinotan, at three different doses (.5mg/day, 1.25mg/day, 2.5mg/day) using an independent groups experimental design (refer to Table 2 and Table 4.B of the Appendices). In total, only a small sample (N < 50) of severe TBI patients was examined, with no sizeable improvement in global outcome (GOS) at three months post-injury evident when this treatment was administered within one day of injury, suggesting that it does not markedly improve outcome following a severe TBI. While the samples for these three studies were of comparable severity, the drug dosages for the three studies did differ. However, at best a small improvement in global outcome (d = .30) was only evident for a 0.5mg/day dose, suggesting that treatment benefits may be dose-dependent.

Catecholaminergic Treatments

A single study, which used an independent groups repeated measures design with a large sample (N = 74), assessed the effects of the dopamine agonist *amantadine* (also known as Symmetrel) at a dose of 400mg/day administered within three days of a severe TBI (see Table 2, also Table 4.B of the Appendices). A very large improvement in arousal, which was measured using the GCS, was apparent at eight to nine days post-injury. The large fail safe N (N_{fs} = 8) suggests that it is unlikely that this finding could be called into question by unpublished studies that have not found any treatment benefit. Thus, following severe TBI, standard therapy (e.g., ventilation, sedation) plus amantadine appears to improve arousal when compared to standard therapy alone.

Table 2: Pharmacological treatments: Weighted effect sizes organised by chemical group, drug and cognitive/behavioural measure.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (days)	Injury Severity	M d_{wss}	SD d_w	Min d	Max d	Nfs	OL%	M d_{wsq}	Study Reference*
SEROTONERGIC TREATMENTS													
BAY X 3702 (Serotonin agonist)													
Independent Groups													
Glasgow Outcome Scale (3 month)	Global Outcome	3	48	1	severe	.04	.25	-.14	.33	0	100	.04	Ohman, et al., 2001 (Study 1 – 3)
CATECHOLAMINERGIC TREATMENTS													
AMANTADINE (Dopamine agonist)													
Independent Groups Repeated Measures													
Glasgow Coma Scale	Arousal	1	74	3	severe	1.86				8	21		Saniova et al., 2004
CALCIUM CHANNEL BLOCKERS													
NIMODIPINE (Calcium Channel Blocker)													
Independent Groups													
Glasgow Outcome Scale (6 month)	Global Outcome	2	916	6 – 9	severe	.10	.13	-.09	.10	0	92	.00	Pillai et al., 2003; The European Study Group, 1994

Cont'd

Table 2 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (days)	Injury Severity	M d_{wss}	SD d_w	Min d	Max d	Nfs	OL%	M d_{wsq}	Study Reference*
NMDA ANTAGONISTS													
GK-11 (NMDA antagonist)													
Independent Groups													
Glasgow Outcome Scale: (3 month)	Global Outcome	3	48	2	severe	-.27	.40	-.03	-.74	0	79	-.28	Lepeintre et al., 2004 (Study 1 – 3)
CP-101,606 (NMDA antagonist)													
Independent Groups													
Glasgow Outcome Scale (6 month)	Global Outcome	1	404	8	severe	.07				1	92		Yurkewicz et al., 2005
Cognitive Abilities Screening	General Cognition	1	404	8	severe	-.03				1	100		Yurkewicz et al., 2005
Disability Rating Scale	Global Outcome	1	404	8	severe	-.07				1	92		Yurkewicz et al., 2005
STEROID TREATMENTS													
METHYLPREDNISOLONE (Corticosteroid)													
Independent Groups													
Glasgow Outcome Scale (6 month)	Global Outcome	2	9654	8 – 72	mild/mod/sev	-.07	.15	-.07	.14	0	92	.02	Crash Trial, 2005; Saul et al., 1981

Cont'd

Table 2 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (days)	Injury Severity	M d_{wss}	SD d_w	Min d	Max d	Nfs	OL%	M d_{wsq}	Study Reference*
PEPTIDE TREATMENTS													
CP-0127 (Peptide)													
Independent groups repeated measures													
Glasgow Coma Scale	Arousal	1	20	2	mild/mod	6.07				29	2		Narotam et al., 1998
Independent groups													
Glasgow Outcome Scale (6 month)	Global outcome	1	133	1	severe	.26				0	79		Marmarou et al., 1999
Glasgow Outcome Scale (3 month)	Global outcome	1	133	1	severe	.21				0	85		10
LF 16-0687Ms (Peptide)													
Independent groups													
Glasgow Outcome Scale (6 months)	Global Outcome	2	25	1	severe	.32	.78	-.24	.87	2	79	.32	Marmarou et al., 2005 (Study 1 – 2)
Glasgow Outcome Scale (3 months)	Global Outcome	2	25	1	severe	.27	.98	-.43	.96	2	79	.27	Marmarou et al., 2005 (Study 1 – 2)
DESMOPRESSIN (Peptide)													
Independent groups repeated measures													
PASAT	Attention	1	17	1	mild	.37				1	73		Filipova et al., 1989

Cont'd

Table 2 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (days)	Injury Severity	M d_{wss}	SD d_w	Min d	Max d	Nfs	OL %	M d_{wsq}	Study Reference*
Story Memory	Memory	1	17	1	mild	.21				0	85		Filipova et al., 1989
CANNABINOIDS													
DEXANABINOL (Cannabinoid)													
Independent Groups													
Glasgow Outcome Scale (3 month)	Global Outcome	2	897	5 – 6	severe	.10	.43	.06	.67	0	92	.36	Knoller et al., 2002; Maas et al., 2006
(6 month)	Global Outcome	1	846	6	severe	.01		.01	.01	0	100		Maas et al., 2006
FREE RADICAL SCAVENGERS													
PEG-SOD (Oxygen Radical Scavenger)													
Independent Groups													
Glasgow Outcome Scale (3 month)	Global Outcome	3	104	3 – 4	severe	.18	.18	.00	.36	2	85	.17	Muizelaar et al., 1993 (Study 1 – 3)
(6 month)	Global Outcome	3	104	3 – 4	severe	.05	.13	-.08	.18	0	92	.05	Muizelaar et al., 1993 (Study 1 – 3)

Note: M d_{wss} = mean effect size weighted for sample size; SD d_w = standard deviation of weighted effect size; Min d_w = minimum weighted effect size; Max d_w = maximum weighted effect size; Nfs = fail safe N; OL% = overlap percent; M d_{wsq} = mean effect size weighted by methodological quality; Ref = study reference number; mod = moderate; sev = severe; PASAT = Paced Auditory Serial Addition Test.

* See Appendix 4.A of the Appendices for reference list of studies that have been analysed

Calcium Channel Blockers (modulators of ion homeostasis)

Two studies examined the neuroprotective effects of the calcium channel blocker *nimodipine* in large samples of severe TBI patients (N = 916) using an independent groups experimental design (Table 2). All of the patients were treated within nine hours of injury (range 6 - 9 hours) at doses of 1mg/hour or 5mg/hour, however, no sizeable treatment benefit was observed when global outcome (GOS) was assessed at six months post-injury (see also the Appendices, Table 4.B). Moreover, as can be seen for the minimum and maximum d_w values, neither dose resulted in sizeable improvements to outcome.

NMDA Antagonists (amino acids)

In total, there were four studies that investigated acute treatment of severe TBI with two anticonvulsants, three examining the non-competitive NMDA antagonist *GK-11* (Gacyclidine) in a small sample (N = 48) and one investigating the highly selective NMDA antagonist *CP-101,606* (Traxoprodil) in a large sample (N = 404) (Table 2). All used an independent groups experimental design. When administered within two hours of injury, GK-11 did not improve global outcome (GOS) at three months post-injury. If anything, there was a subtle deterioration. Different dosages of GK-11 were examined (.01mg/kg, .02mg/kg, .04mg/kg) by Lepeintre et al. (2004, Study 1 - 3). A moderately large negative treatment effect (d = -.74) was found at a dose of .01ml/kg, suggesting that poorer outcome was associated with lower doses. However, each of these dosages were only trialled in small samples ($N_{participants}$ = 11 to 13).

In addition, CP-101,606 administered at a dose of .75mg/kg within an average of eight hours of a severe TBI did not improve global outcome (6 month GOS; Disability Rating Scale) or cognition (Cognitive Abilities Screening Test) (see also Table 4.B of the Appendices). The evidence, therefore, suggests that when given acutely, neither GK-11 nor CP-101,606 improves global outcome or cognition (in the case of CP-101,606) in comparison

to placebo control groups, with lower doses of GK-11 being potentially associated with poorer outcome.

Steroid Treatments

The steroid treatment *methylprednisolone* (Medrol) was investigated in two studies of mild, moderate and severe TBI patients at doses of 2g/hour and 5mg/day using an independent groups experimental design (refer to Table 2). Overall, a very large sample of participants (N = 9654) was recruited, all of whom were treated within 72 hours of injury (8 - 72 hours). Global outcome, as measured by the GOS at six months post-injury was not measurably improved by treatment with methylprednisolone (see also Table 4.B of the Appendices).

Peptide Treatments

Three peptide treatments, the bradykinin receptor antagonist *CP-0127* (Bradycor) and *LF 16-0687Ms* (Anatibant), as well as the anti-diuretic *Desmopressin* (DDAVP) were examined using either an independent groups repeated measures or an independent groups experimental design (see Table 2). All were administered between one and two days after mild, moderate, or severe TBI. When treatment with CP-0127 at a dose of 3mg/kg/min was examined in a single study of mild to moderate TBI patients using an independent groups repeated measures experimental design, very large treatment benefits were noted for arousal (GCS). However, when CP-0127 was administered at a dose of 3Ug/kg/min there were no treatment benefits for global outcome (GOS) at three or six months post-injury using an independent groups experimental design (see also Appendices, Table 4.B).

Additionally, two studies with small samples investigated treatment with LF 16-0687Ms in severe TBI at doses of 3.75mg or 22.5mg. No sizeable treatment benefits for global outcome (GOS) were found at three or six months post-injury using an independent groups experimental design (see also Appendices, Table 4.B). However, as seen from the

minimum and maximum *value* for LF 16-0687Ms, the treatment effects for different dosages varied markedly (*d* = -.24 and -.43, dose minimum; *d* = .87 and .96, dose maximum), suggesting that higher doses are associated with some treatment benefits.

Finally, no sizeable improvements to cognition (attention and memory) were found for the antidiuretic Desmopressin (DDAVP) when administered at a dose of 20mg/day following mild TBI according to a study that used an independent groups repeated measures experimental design (refer also Appendices, Table 4.B).

Cannabinoids

The cannabinoid *dexanabinol* has been investigated for use in severe TBI at doses of 48mg/day and 150mg/day in two studies that used an independent groups experimental design (refer to Table 2, Table 4.B of the Appendices). In combination, these studies only revealed a very small benefit (*d* = .1) to global outcome (GOS) at three months post-injury. However, one study revealed a moderate to large treatment benefit (*d* = .67) for its small sample of participants (N = 30) when a dose of 48mg/day was administered within 6 hours of injury. The other study, which used a much higher dose (150mg/day) revealed negligible benefits (*d* = .06), albeit in a larger sample (N = 428). Nonetheless, when considered in toto, global outcome (GOS) did not improve with treatment at either three or six months post-injury.

Free Radical Scavengers

A single oxide scavenger, PEG-SOD (Pegorgotein) was examined by three small scale studies of severe TBI (N = 25 to 27), each of which used an independent groups experimental design (Table 2). When treatment was administered within four hours of injury no sizeable treatment effects were observed for the GOS at either three or six months. Moreover, no marked treatment effects were found for the different dosages of PEG-SOD that were evaluated in these studies (2,000U/kg, 5,000U/kg or 10,000U/kg), suggesting that the acute administration of this drug does not improve long-term outcome following a severe TBI.

Discussion

The current study analysed data from a total of 22 clinical studies investigating the cognitive and behavioural effects of 11 pharmacological treatments administered in the acute stage after a TBI. The final data set included 12,932 persons who had sustained a TBI, 6,472 of whom were treated with a pharmacological agent and 6,460 controls who received either no treatment or a placebo. The majority of participants were males, and the average age was approximately 34 years for the treatment group and 32 years for the control group, which is consistent with the fact that younger people are more likely to sustain a TBI (Elovic & Zafonte, 2005; Lee, et al., 2003; Silver, et al., 2005). In total, six measures of cognitive and behavioural outcome were used to evaluate the effects of these treatments, one measure of arousal (GCS), three measures of cognition (attention, memory, general cognition), and two measures of global outcome (GOS, Disability Rating Scale). Our analysis of the available data demonstrated that the treatment and control groups were well matched in terms of patient age, injury severity and time from injury-to-treatment, suggesting that differences in these variables did not contribute to the findings.

In order for a pharmacological agent to improve outcome following TBI, we argued that it had to show moderate ($d \geq .5$) to large treatment effects ($d \geq .8$), which could not be drawn into question by the tendency for journals to only publish significant findings (N_{fs}). In addition, an independent groups repeated measures experimental design was thought to control for a larger number of confounding variables (practice effects on cognitive tests, spontaneous recovery, and differences in baseline performance), thereby increasing our confidence in the finding. When these criteria were applied to all of the pharmacological treatments investigated in this meta-analysis, there were two treatments that were of note.

First, a marked improvement in arousal was found for the dopamine agonist *amantadine*. When this drug was administered for a period of three days post-injury to

comatose patients who had sustained a severe TBI at a dose of 400mg/day there was a sizeable improvement in arousal (GCS). This supports an association between decreased levels of brain dopamine and impairments in arousal and cognition (Napolitano, et al., 2005; Silver, et al., 2005). In addition to its actions as a dopamine agonist, amantadine is also thought to act as a direct NMDA receptor antagonist, which may reduce glutamate induced excitotoxicity and associated brain swelling following TBI (Kraus & Chu, 2005; Saniova, Drobny, Kneslova, & Minarik, 2004). Thus early treatment with *amantadine* may improve arousal by simultaneously minimising disruptions to dopamine levels in the brain and by reducing excitotoxicity and associated brain swelling.

Second acute treatment of mild to moderate TBI with the anti-inflammatory bradykinin B2 receptor antagonist *CP-0127* (Bradycor) resulted in reduced intracranial pressure (ICP) and an associated improvement in arousal (GCS). While a significant increase in arousal and a decrease in ICP to < 20mmHg was found following a seven day infusion of CP-0127, a rise in ICP is unlikely in most cases of mild and some cases of moderate TBI (Marion, 1999; Silver, et al., 2005). Nonetheless, the significant and sustained rise in ICP with an associated deterioration in neurological condition that was noted in the placebo control group suggests that a more severe injury occurred than was indicated by the initial GCS score. While prior research in rodents has found that anti-inflammatory treatments effectively minimise post-injury rises in brain oedema (and consequently ICP) and its associated impairments in cognition (Kaplanski, 2002; Panikashvili, et al., 2001), CP-0127 was the only bradykinin antagonist investigated that produced a sizeable treatment effect. Indeed, the alternative highly-specific bradykinin B_2 antagonist, *LF 16-0687Ms* (Anatibant), did not show this improvement. Nonetheless, our analysis supports that the early administration of bradykinin B_2 receptor antagonists may be worthwhile in terms of minimising the inflammatory response and reducing increased ICP, thereby improving arousal following TBI.

With respect to treatments that were evaluated in terms of their impact on cognition, neither the highly selective NMDA antagonist *CP-101,606* (Traxoprodil) nor the anti-diuretic *desmopressin* (DDAVP stimate) were associated with significant improvements in general cognition following a severe TBI, or attention and memory following a mild TBI, respectively. While this suggests that cognitive outcome may not benefit from acute treatment with these agents, each treatment was only examined by one study indicating a need for their further empirical evaluation.

In contrast, there were 9 treatments that were evaluated in terms of their impact on global outcome. While improvements in GOS were found for *BAY X 3702* (Repinotan) at three months post-severe TBI, *nimodipine* and *CP-101,606* (Traxoprodil) at six months post-severe TBI, and *CP-0127* (Bradycor), *LF 16-0687Ms* (Anatibant), *dexanabinol* and *PEG-SOD* (pegorgotein) at three and six months post-severe TBI, the treatment benefits were only small. Additionally, small negative treatment effects were found for the non-competitive NMDA antagonist *GK-11* (Gacyclidine) and *methylprednisolone*. However, moderate to large treatment benefits were found on the GOS following severe TBI by three studies that administered different drugs. Specifically, moderate treatment benefits were found by one study examining three month global outcome after administering a single 48 mg/day dose of *dexanabinol*, large benefits were found by another study that examined three and six month global outcome following a single injection of the bradykinin antagonist *LF 16-0687Ms* (Anatibant) at a dose of 22.5 mg/kg, while two .01 ml/kg doses of the non-competitive NMDA antagonist *GK-11* (Gacyclidine) was associated with a much poorer outcome at three months post-injury in a single study. These agents may, therefore, have dose-dependent treatment effects that still need to be resolved. Moreover, males were reported to have a much greater improvement in global outcome (GOS) following treatment with the highly selective NMDA antagonist *CP-101,606* (Traxoprodil) than their female counterparts

(Yurkewicz, et al., 2005), suggesting that this drug may have gender specific treatment effects.

Limitations of the Current Study

There are a number of limitations to the current findings. Specifically, the inclusion of studies published only in English may have reduced the number of studies that were available to analyse. In addition, some relevant studies may have been excluded because electronic searches identify search term matches with words in the title, abstract and keyword listing. A large number of search terms were, therefore, used and the bibliographies of all retrieved articles were additionally searched to reduce the likelihood of missing relevant studies.

Additionally, four studies did not report data that could be converted into an effect size (Giannotta, et al., 1984; Levin, 1991; The British/Finnish Co-operative Head Injury Trial Group, et al., 1990; Wolf, et al., 1993). While written requests for additional data were made, this largely proved to be unsuccessful because authors did not respond, could not be located, or research data was discarded seven years from the date of publication, resulting in the necessary exclusion of these studies. This highlights the need for all authors to report basic summary data (means and standard deviations) in their results. Moreover, an independent groups repeated measures experimental design controls for the effects of more potentially confounding variables and, as a result, more confidence can be placed in the findings of studies that used this experimental design. Unfortunately, only three out of 22 studies used such a design.

Injury severity data (GCS, PTA, LOC), level of education (a proxy measure of pre-morbid cognitive ability), and time from injury to treatment, are all needed to allow a thorough critique of a study. However, no studies reported all of this information. Moreover, treatment benefits were often found in specific samples (i.e., mild/moderate, severe TBI) raising questions about whether these findings can be generalised to individuals with injuries

of greater or lesser severity. With respect to drug dosage, studies that used the same treatment and outcome measure often reported drug dosages in different metrics (i.e., mg/kg, mg/day). A consistent level of measurement for drug dosage would improve the ease with which the findings from different studies can be compared. Finally, where sizeable treatment benefits were found in the current meta-analysis, they were often only based on a single study. These treatments, therefore, require further empirical investigation.

Conclusions

A range of different pharmacological treatments have been used in the acute phase of an injury to treat cognitive and behavioural problems caused by TBI. Only two of these treatments, the dopamine agonist *amantadine* (Symmetrel) and the bradykinin B2 antagonist *CP-0127* (Bradycor), improved outcome after TBI. Specifically, treatment with *amantadine* markedly improved acute arousal (GCS) in comparison to an untreated control group following a severe TBI, while *Bradycor* minimised reductions in acute arousal (GCS) in comparison to a placebo control group following a mild to moderate TBI. Both of these treatments were investigated using an independent groups repeated measures experimental design. While none of the remaining treatments that were examined here were associated with an overall improvement in global outcome (GOS) or cognition when studies were combined, both the bradykinin antagonist *LF 16-0687Ms* (anatibant) and the cannabinoid *dexanabinol* were associated with a dose-dependent improvement in three and six month global outcome, while the amino acid *GK-11* (gacyclidine) was associated with a dose-dependent impairment in three month global outcome. Importantly, these findings indicate that different drug dosages may have varying outcomes and that different cognitive and behavioural measures may be differentially sensitive to the effects of these treatments, highlighting the importance of examining multiple doses and a range of treatment outcomes.

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Appendices

Figure 4.1: Details of electronic database searches

Table 4.A: Key search terms used in database searches

Table 4.B: Demographic data, treatment and cognitive or behavioural tests used for each study included in the human meta-analysis

Table 4.C: Chemical group, pharmacological category and method of action of drugs

Table 4.D: Methodological quality rating system

Appendix 4.A: Reference list for all studies included in the meta-analysis

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Chapter 5 :Impact of pharmacological treatments on cognitive and behavioural outcome in the post-acute stage of adult traumatic brain injury: A meta-analysis

The previous study (Chapter 4) found that early treatment with one anti-inflammatory (Bradycor) and one dopamine agonist (amantadine) improved arousal in a clinical population following TBI. Although none of the treatments that were administered in the early stages improved long-term outcome, it is uncertain whether treatments administered in the post-acute stage of injury (≥ 4 weeks post-injury) improve recovery. The final meta-analysis was therefore undertaken to integrate and compare the findings from clinical research of post-acute treatments.

While it was intended that only those treatments that were administered in the post-acute period (i.e. ≥ 4 weeks post-injury) would be included, a large number of studies investigated treatment shortly before, and spanning the post-acute period after a TBI. These studies may also provide important information regarding the long-term efficacy of pharmacological treatments. To ensure that there was minimal overlap between this study and the previous study, only those findings from studies that administered treatment more than three days post-injury were included. In addition, as these treatment benefits are more likely to be influenced by spontaneous recovery, the findings are presented separately from those studies that administered treatment a month or more after an injury. For consistency, the system for categorising treatments in Study 2 was also used here.

TITLE: Impact of pharmacological treatments on cognitive and behavioural outcome in the post-acute stage of adult traumatic brain injury: A meta-analysis

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Abstract

Pharmacological treatments that are administered to adults in the post-acute stage after traumatic brain injury (TBI) (≥ 4 weeks post-injury) have the potential to reduce persistent cognitive and behavioural problems. While a variety of treatments have been examined, the findings are difficult to evaluate due to the use of different research methodologies and measures of efficacy, thereby hampering advances in the treatment of TBI. An examination of research that has investigated the cognitive and behavioural effects of pharmacological treatments administered in the post-acute stage after TBI was therefore conducted and treatment effects calculated. The PubMed and PsycInfo databases were searched using 35 terms. Cohen's *d* effect sizes, percent overlap and fail-safe N statistics were calculated for each treatment. Both randomised controlled trials and open-label studies (prospective and retrospective) were included and the results of different experimental designs examined separately due to differences in the Cohen's formulae for these designs. Nineteen treatments were investigated by 30 independent studies, comprising 395 participants with TBI in the treatment groups and 137 TBI controls. When treated in the post-acute period, one dopaminergic agent (methylphenidate) improved behaviour (anger/aggression, psychosocial function) and one cholinergic agent (donepezil) improved cognition (memory, attention). In addition, when the injury-to-treatment interval was broadened to include studies that administered treatment just prior to the post-acute period, two dopaminergic agents (methylphenidate, amantadine) showed clinically useful treatment benefits for behaviour, while one serotonergic agent (sertraline) markedly impaired cognition and psychomotor

speed. These findings were based on single small sample studies and require further empirical evaluation.

Keywords: post-acute, pharmacological treatment, traumatic brain injury, outcome, meta-analysis

Running Title: Post-acute pharmacotherapy and TBI

Introduction

Traumatic brain injury (TBI) is a primary cause of injury-related death and disability (Engel, Slemmer, Vlug, Maas, & Weber, 2005; Marsh & Sleigh, 2002). Alterations to the chemistry and structure of brain cells following TBI may cause long-term changes to the levels of neurotransmitters, which can lead to the development of a variety of cognitive and behavioural problems (Phillips, Devier, & Feeney, 2003; Preston, O'Neil, & Talaga, 2005). One target for the treatment of TBI has been to limit or reduce these neurochemical changes using pharmacological interventions. Whereas treatments that are administered soon after a TBI are thought to improve outcome by reducing early neurochemical disturbances, treatments given in the post-acute stage (i.e., $\geq$ 4 weeks post-injury) are likely to improve cognitive and behavioural outcome by minimising the effects of long-term neurochemical changes. A recent meta-analysis of the efficacy of pharmacological treatments administered in the hours and days following adult TBI (< 7 days post-injury) has found that a number of treatments improve outcome (Wheaton, Mathias, & Vink, 2009), however, it remains unclear whether treatments administered in the weeks and months post-injury can also improve outcome.

Although a wide range of pharmacological treatments have been given in the post-acute stage after adult TBI for the purpose of treating persistent cognitive and behavioural problems, the findings are inconsistent (Pliszka, 2003; Silver, McAllister, & Yudofsky, 2005). For example, while anxiety and depression have improved and combative behaviour decreased following treatment with both *serotonergic* (e.g., fluoxetine, sertraline, amitriptyline) (Cassidy, 1989; Fann, Uomoto, & Katon, 2000; Horsfield, et al., 2002; Lee, et al., 2005; Mysiw, Jackson, & Corrigan, 1988) and *dopaminergic* agents (amantadine, methylphenidate, bromocriptine) (Chandler, Barnhill, & Gualtieri, 1988; Gualtieri & Evans, 1988; Karli, et al., 1999; Nickels, Schneider, Dombovy, & Wong, 1994), contradictory

findings have also been reported (Cassidy, 1989; Horsfield, et al., 2002; Karli, et al., 1999; Nickels, et al., 1994). Similarly mood and behaviour have been found to improve with the *cholinergic* treatment donepezil (Masanic, Bayley, vanReekum & Simmard, 2001), while improved mood and reduced levels of anxiety and combativeness have been found with the *modulator of ion homeostasis* carbamazepine and the *anticonvulsant* divalproex (Azouvi, et al., 1999; Beresford, Arciniegas, Clapp, Martin, & Alfers, 2005; Kim & Humaran, 2002). In addition, global outcome has reportedly improved with a range of *dopaminergic* agents (e.g., amantadine, methylphenidate) (Kaelin, Cigu, & Matthies, 1996; Meythaler, Brunner, Johnson, & Novak, 2002; Whyte, et al., 1997), although long-term functional recovery has not always been evident (methylphenidate) (Plenger, et al., 1996).

Neurochemical changes following TBI may also lead to cognitive problems, including impairments in learning, memory and attention (Napolitano, Elovic, & Qureshi, 2005). Although cognitive problems have been shown to improve with *serotonergic* (e.g., fluoxetine, sertraline, amitriptyline) (Fann, Uomoto, & Katon, 2001; Horsfield, et al., 2002; Jackson, Corrigan, & Arnett, 1985), *dopaminergic* (e.g., amantadine, methylphenidate) (Kraus & Chu, 2005; Lee, et al., 2005; Saniova, Drobny, Kneslova, & Minarik, 2004), and *cholinergic* agents (donepezil, combined treatment with physostigmine and lecithin) (Kaye, Townsend, & Ivins, 2003; Khateb, Ammann, Annoni, & Diserens, 2005; Levin, et al., 1986; Zhang, Plotkin, Wang, Sandel, & Lee, 2004), there are also contradictory findings (amantadine, methylphenidate) (Nickels, et al., 1994; Speech, Rao, Osmon, & Sperry, 1993; Whyte, et al., 1997). Improvements in cognition have also been found with the *anticonvulsant* valproate and the *phospholipid intermediate* CDP-choline (Leon-Carrion, Dominguez-Roldan, Murillo-Cabezas, Dominguez-Morales, & Munoz-Sanchez, 2000), however, valproate has been associated with an increase in fatalities (Dikmen, Machamer, Winn, Anderson, & Temkin, 2000). Moreover, cognition has improved with some *peptides* (lysine vasopressin,

desmopressin, cerebrolysin) (Alvarez, et al., 2003; Eames & Wood, 1999; Filipova, Jung, & Krejcova, 1989), but not others (vasopressin, desmopressin) (Fewtrell, House, Jamie, Oates, & Cooper, 1982; Jenkins, Mather, Coughlan, & Jenkins, 1981; Reichert & Blass, 1982).

Variability between studies with respect to the pharmacological treatment and experimental design (e.g., use of a control group, whether pre-injury and/or post-injury assessments are completed), as well as differences in the cognitive and behavioural measures that are used to assess efficacy, makes it difficult to consolidate these findings (Tilley, 1996). For example, various pharmacological treatments in each of a number of different drug classes (e.g., serotonergic, dopaminergic, cholinergic) have been examined and these vary in terms of their neurochemical effects. Researchers have also used different experimental designs (i.e., independent groups, repeated measures, and cross-over designs; randomised controlled trials and open-label studies), which differentially control for confounding variables (e.g., placebo effects, test practice effects, spontaneous recovery). Additionally, cognitive and behavioural outcome has been evaluated using a wide variety of tests that use different scales of measurement (i.e., continuous, discrete) and may vary in their sensitivity to treatment effects (Satz, et al., 1998). Moreover, there are a variety of methodological variables (e.g., age, injury severity, post-injury treatment interval, drug dosage) that impact on the research findings (Filipova, et al., 1989; Lepeintre, et al., 2004; Silver, et al., 2005). Finally, variability with respect to the number of participants recruited may impact on the likelihood of finding a significant treatment effect, with a statistically significant effect more likely to be detected in a larger sample (Tilley, 1996).

Effect sizes provide an objective and quantitative means by which to evaluate the findings of this research, thereby allowing the efficacy of different treatments to be directly compared and evidence-based treatment recommendations to be formulated. The current study, therefore, undertook a meta-analysis to evaluate the impact of pharmacological

treatments that were administered in the post-acute stage on cognitive and behavioural outcome following TBI. This study extends the findings of a recent meta-analysis which examined the impact of pharmacological treatments administered in the early stage after a TBI on cognitive and behavioural outcome (Wheaton, et al., 2009).

Method

Search Strategy and Selection Criteria

The PsychINFO and PubMed electronic databases were searched from January 1980 to April 2010 in order to identify all prospective and retrospective studies (including randomised clinical trials and open-label studies) that examined pharmacological treatments for cognitive and behavioural problems following TBI. The search was kept broad to ensure that all relevant articles were captured (N = 35 terms; Table 5.A, of the Appendices for key terms used in database searches). The reference lists of all retrieved studies were also examined to ensure that all relevant studies were identified.

A study was included for analysis if it met the following criteria: (a) was published in a journal; (b) was in English; (c) was not a case study; (d) had treatment and control group data for participants who had sustained non-penetrating TBIs (Note: in a single sample repeated measures design, participants act as their own control); (e) participants were aged 16 years or older. Where age ranges were not reported, a study was deemed eligible for inclusion if the mean age +/- one standard deviation met these criteria; (f) no participant was known to have: sustained a previous TBI; had physical, visual or language impairments that could independently affect test performance; a pre-existing psychiatric or neurological disorder (e.g., schizophrenia, dementia); or a past or present history of substance abuse; (g) participants were administered the one or more measures of cognition and/or behaviour; (h) a

pharmacological agent was administered to the treatment group in the post-acute (≥ 4 weeks post-injury) stage following injury TBI. Given the subjective nature of this cut-off, if some participants were treated prior to this period (mixed treatment interval), these studies were included but analysed separately; and (i) the format of the reported results enabled the calculation of an effect size (i.e. means, standard deviations, *t* tests, one-way *F* statistics, exact *p* values) or this information was provided by authors in response to a written request. Where raw data were reported, these were converted to means and standard deviations. It was not possible to additionally screen studies for the use of other pharmacological agents (e.g., antipsychotics, neuroleptics) because these data were not consistently reported. However those studies that did report this information are identified in the Results section and in the relevant tables.

The literature searches identified 13,857 articles (Figure 5.1 of the Appendices for details of electronic database searches). When the inclusion criteria were initially applied to the titles and abstracts of these articles, 99 studies were identified as potentially relevant. Retrieval of the full-text versions of these studies, and a re-application of the inclusion criteria, revealed that 70 did not meet one or more of the inclusion criteria, leaving 29 studies that examined 19 different treatments. The bibliographies of all retrieved articles were also examined. This did not identify any additional studies. Eight studies failed to report data that was needed in order to calculate effect sizes (Cardenas, et al., 1994; Kaelin, et al., 1996; Morey, Cilo, Berry, & Cusick, 2003; Nickels, et al., 1994; Reichert & Blass, 1982; Saran, 1985; Whyte, et al., 2004; Whyte, et al., 2008). Written requests for these data were made to the corresponding Authors in all eight cases, however these requests were unsuccessful because the authors could not be located or did not respond, or data had been discarded seven years from the date of publication, necessitating their exclusion.

When combining effect sizes, the participants in each study are required to be independent of those that are used in other studies (Hunter, Schmidt, & Jackson, 1982; Rosenthal, 1995). One study (Lee, et al., 2005) that examined two different treatments in two independent samples was therefore treated as two studies. Thus, effectively, the data for 30 independent studies were analysed. Detailed demographic and bibliographic details for each study, together with the study designs and outcome measures, are provided in Table 5.B of the Appendices for tests used included in the meta-analysis.

Research Designs

Four research designs were used to examine treatment effects. Firstly, an *independent groups repeated measures design* included blinded (single and double) and unblinded randomised clinical trials, that assessed two groups (Treatment, Control) on two occasions (pre- and post-treatment), and compared group differences in pre-post treatment change. Secondly, an *independent groups design*, which included both double-blinded randomised control trials and open-label studies, involved comparing the post treatment outcome of two groups (Treatment, Control). Thirdly, a *repeated measures design* (single-blinded or open-label) compared the pre- with the post-treatment performance of a single treatment group (Morris & DeShon, 2002). Finally, in a *cross-over design*, two groups each acted as both treatment and control groups during the course of the study (Dallal, 2000; Garcia, Benet, Arnau, & Cobo, 2004). This design involves a double-blinded randomised control trial which can be operationalized in one of two ways. In the first, two groups (Treatment, Control) were assessed in stage one, followed by a wash-out period and a reversal of the treatment and the control groups. Alternatively, a single group of individuals systematically alternated between the treatment and control conditions without a wash-out period.

Of these designs, only an *independent groups repeated measures* and an *independent groups design* minimise the confounding of treatment effects with spontaneous recovery

and/or improvements to test performance as a consequence of practice effects (Morris & DeShon, 2002). In addition, treatment and control groups can be matched on demographic variables. The independent groups repeated measures design also controls for group differences in baseline performance, thereby making it a better experimental design for evaluating the efficacy of a treatment. As different formulas are used for the calculation of effect sizes for each research design, the results were treated separately (Morris & DeShon, 2002). Of additional concern, non-blinding and non-randomisation of participants and/or assessors are generally associated with larger treatment effects (Hrobjartsson & Gotzsche, 2001; Schulz, Chalmers, Hayes, & Altman, 1995), particularly when subjective measures of outcome are used (e.g., questionnaires) (Hrobjartsson & Gotzsche, 2001). Double-blinding and randomisation therefore increase our confidence in a treatment effect by minimising the risk that participant or assessor expectations or foreknowledge of group allocation have influenced the results. Finally, treatment effects that are based on retrospective chart reviews may be limited by variability in the quality of the data that is available for inclusion (Gearing, Mian, Barber, & Ickowicz, 2006).

Data Preparation

There were some cases where cognitive or behavioural measures were administered on multiple occasions (e.g., during or following treatment, or before and after a washout period). As some of these assessments were not consistent with the purpose of this study, a number of criteria were used to determine which data would be analysed. Firstly, some studies assessed outcome on more than one occasion during or following treatment which, if averaged, may have impacted on the resulting effect size (e.g., if there were large treatment effects early and small effects at the end, the average would be larger than a final post-treatment effect). As not all studies assessed outcome repeatedly, only data from the final session at the end of, or after completion of, the treatment were used in the calculation of effect sizes. One exception

to this was a cross-over study by Wroblewski, Joseph, & Cornblatt (1996), where two independent groups (Treatment, Control) were assessed in stage one but only the placebo controls were crossed over in the second stage. In this case, an effect size was calculated using data at the end of the first stage of treatment.

Secondly, a *cross-over design* may be susceptible to carry-over treatment effects (i.e. a persistent treatment effect that carries over to the next period), which could minimise the differences between the treatment and control conditions. For this reason, where a treatment and placebo were initially administered to two independent groups, followed by a wash-out period and a reversal of the groups, and the pre- and post-treatment data for each treatment period were reported separately for both groups, only data from the first treatment period were included in the analysis. The potential confounds of practice, spontaneous recovery and between-group differences in baseline performance were minimised by treating these data as an independent groups repeated measures experimental design. Four studies were treated in this manner (Levin, et al., 1986; Meythaler, et al., 2002; Wroblewski, et al., 1996; Zhang, et al., 2004). Where a *cross-over design* was used and the pre- and post-crossover data were *not* reported independently (i.e., only final mean scores for each group were reported), these data were treated as cross-over studies. Three studies were treated in this way (Speech, et al., 1993; Whyte, et al., 1997; Willmott & Ponsford, 2009).

Finally, when two separate pharmacological treatments, with different methods of action, were administered to the same group of participants, and these treatments were separated by a wash-out period, effect sizes were calculated for each treatment separately to measure efficacy. The use of baseline scores for each treatment period assisted in reducing the potential impact of carry-over effects and practice effects. One study (Saran, 1988) was treated in this manner.

Each of the treatments that were included in this study were categorised into a chemical group, pharmacological category, and primary mode of action (Table 5.C of the Appendices for the categorisation of all pharmacological treatments]). This system was adopted to simplify the presentation of data and is not intended to imply that the method of action of these drugs is limited to a single chemical group. Moreover, it does not affect the results of this study, because the results for different treatments are not combined, only their presentation.

Statistical Analysis

Cohen's *d* effect sizes were calculated in such a way that a positive *d* always indicated that a treatment improved cognition or behaviour. Cohen's *d* provides a measure of the standardised difference between two means. A different method for calculating the standard deviation is needed for each design (i.e., repeated measures & independent groups repeated measures designs: pre-treatment standard deviation (Morris & DeShon, 2002), independent groups designs: pooled standard deviation (Zakzanis, 2001), cross-over designs: control group mean (Lucassen, Assendelft, et al., 1998). According to Cohen's criterion (Cohen, 1977, 1992) a small effect is defined as $d = .2$, a moderate effect as $d = .5$, and a large effect as $d = .8$, where an effect size of .5 indicates that there is a difference of one half of a standard deviation between the mean scores of the two groups. If means and standard deviations were not provided, *t* values, one-way *F* statistics and exact *p* values were converted to *d* (Lipsey & Wilson, 2001; Zakzanis, 2001).

Effect sizes were calculated in multiple stages. Firstly, an effect size was calculated for each outcome measure (cognition, behaviour) that was reported by a study. If a study provided multiple subscale scores for the one measure without providing a total score, effect sizes were calculated for each subscale and then averaged to provide a single score. The

effect sizes that were obtained from different studies that used the same measure were then averaged to examine treatment effects.

Sample size can affect the reliability of an effect size, with greater variability and consequently less confidence placed in the findings from small sample studies (Hunter & Schmidt, 2004; Lipsey & Wilson, 2001; Rothstein, et al., 2005). While weighting effect sizes by the inverse of the variance provides one method for addressing the bias associated with sampling variance (Hunter & Schmidt, 2004), not all studies provided the data that was need for this calculation (e.g., a correlation between the pre- and post-treatment scores). Therefore, where studies were combined, it was only possible to provide an overall weighted mean effect size by weighting each of the effect sizes from individual studies by its sample size and then averaging them. Six studies were weighted in this way (Dinan & Mobayed, 1992; Kim, Kim, Shin, Park, & Lee, 2009; Saran, 1988; Speech, et al., 1993; Whyte, et al., 1997; Zhang, et al., 2004). In addition, all studies were rated for methodological quality (see Table 5.B of the Appendices for the methodological scale and study ratings). While it was intended that studies would also be weighted for methodological quality, there were limited numbers of studies using the same type of design and measure; seriously limiting the usefulness of such an analysis.

Percentage overlap scores (%OL) were additionally calculated to measure the extent to which there was an overlap in the test scores from the two groups (d = 0 signifies 100% overlap and a d = 4.00 equates to 2.3% overlap) (Zakzanis, et al., 1999). As only one study (Walker, et al., 2004) reported the data that was necessary for calculating ninety-five percent 95% confidence intervals (standard deviations or the correlation between pre- and post-treatment scores), minimum and maximum effect sizes are reported. Finally, fail-safe Ns (N_{fs}) were calculated by multiplying the average effect size by the number of studies that contributed to that value, minus a criterion value that represents a small effect (d = 0.2), and

dividing the end result by 0.2 (Zakzanis, 2001). This statistic addresses the bias toward publishing studies with significant findings by indicating the number of unpublished studies with non-significant treatment effects that are needed to reduce the current finding to a small effect (i.e., $d \leq .2$) and, therefore, call the current findings into question (Rosenthal, 1995; Zakzanis, 2001).

Data Interpretation

Weighted mean Cohen's *d* effect sizes (SD, minimum/maximum) were calculated for each cognitive and behavioural outcome measure that was used to evaluate the 21 treatments. The conclusions that are drawn from this comparison are based on the combined interpretation of the Cohen's *d*, N_{fs} and %OL statistics. It is argued that a clinician could be more confident that a treatment has improved outcome if there were at least moderate improvements in outcome ($d_w \geq .5$) and if it is unlikely that there would be a sufficient number of unpublished studies to draw the current findings into question (i.e. large N_{fs}). Additionally, as an independent groups repeated measures design, followed by an independent groups design, are more rigorous experimental designs, greater weight was placed on the results of studies that used these designs. Finally, as new treatments may only have been investigated by a single study, the results of treatments that were evaluated by both multiple and single studies are provided here.

The findings for each chemical group are presented separately. This is followed by the cognitive and behavioural outcomes for each drug within these groupings, rank ordered by study design (i.e. independent groups repeated measures, independent groups, repeated measures, cross-over design) and effect size (largest to smallest). The results from studies that administered a pharmacological treatment in the post-acute stage (> 4 weeks post-injury) are discussed first, followed by the findings from studies that administered treatment to some participants just prior to, and spanning, this period.

Results

The data for 532 participants from 30 studies were analysed (Table 1), comprising 395 persons with a TBI undergoing treatment (71% male, 29% female) and 137 persons with a TBI acting as controls (72% male, 28% female). A total of 23 studies (22 prospective, one retrospective) examined treatments that were administered in the post-acute stage after TBI. Seven of these used an independent groups repeated measures experimental design, fourteen used a repeated measures design, and two a cross-over design. A further seven studies investigated treatments that were administered to some participants just prior to and spanning the post-acute period (six prospective, one retrospective studies), three using an independent groups repeated measures design, one using an independent groups design, two a repeated measures design, and one a cross-over design. There were ten randomised control double-blinded studies, one randomised control single-blinded study, seventeen open-label studies and two randomised controlled studies that did not report whether blinding occurred (Table 2, see also Table 5.B of the Appendices for specific study details]).

Table 1: Demographic and injury data for the TBI treatment anbd placebo control groups.

	TBI TREATMENT						TBI CONTROLS					
	$N_{studies}$	$N_{participants}$	M	SD	Range		$N_{studies}$	$N_{participants}$	M	SD	Range	
					Min	Max					Min	Max
Participants	30	395	13.2	7.8	3.0	40.0	12	137	11.4	5.2	4.0	20.0
Age (years)	23	316	34.8	8.0	22.7	57.5	8	81	33.4	4.9	25.2	40.2
Education (years)	8	117	12.2	1.1	10.1	13.7	5	50	12.1	1.3	11.0	14.0
GCS	11	174	6.8	2.7	5.3	14.0	3	35	6.5	2.2	4.5	8.9
PTA (hours)	5	94	2849.3	3090.8	192.0	8136.0	1	8	1456.8			
LOC (days)	3	33	20.6	4.9	16.0	25.8	1	8	21.5			
Time from injury (days)	20	273	469.3	569.0	31.0	1896.0	8	81	299.8	463.8	30.0	1314.0

Note: $N_{participants}$ = total number of participants contributing to M = mean, SD = standard deviation and Range; $N_{studies}$= total number of studies contributing to M = mean, SD = standard deviation and Range; GCS = Glasgow Coma Scale; PTA = duration of post-traumatic amnesia; LOC = duration of loss of consciousness.

Twenty-four studies matched individuals on age, 18 on injury severity, 18 on gender, and seven on education. The remaining six studies did not report this information. Most studies recruited individuals with a moderate to severe TBI (53%), while the remainder had a mild, moderate or severe injury (47%).Less than a half of the studies reported specific injury severity data (i.e., GCS: N = 11; PTA: N = 5, LOC: N = 3) or education level (N = 8), and less than 70% reported the average injury-to-treatment interval (N = 20) (see Table 1), thereby precluding any useful comparison of groups on these variables. Only treatments and outcomes associated with moderate to large effect sizes (ie., $d \geq .5$) are presented in Tables 2 (post-acute treatment) and 3 (prior to, and spanning the post-acute stage). Full details of all of the results are reported in the Appendices (Tables 5.D to 5.I for full results for all pharmacological treatments included in the study).

Pharmacological treatments

Serotonergic Treatments

Five studies investigated the post-acute treatment of TBI with five serotonergic agents: one examined *desipramine* (Wroblewski, et al., 1996), two examined *amitriptyline* (Dinan & Mobayed, 1992; Saran, 1988), and one study each examined *phenelzine* (Saran, 1988), and combined treatment with *citalopram* and *carbamazepine* (Perino, Rago, Cicolin, Torta, & Monaco, 2001). Only one study (Wroblewski, et al., 1996) used an independent groups repeated measures design, with the remaining four using a less rigorous repeated measures design (see Appendices, Table 5.B). All studies recruited small samples ($N \leq 23$) of persons with either a mild or severe TBI. One study reported including participants concurrently on psychoactive medications (Wroblewski, et al., 1996) and another included individuals that used the sedative temazepam at night (Dinan & Mobayed, 1992).

Table 2: Teatments administered in the post-acute stage with moderate to large effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL %	Study Reference
SEROTONERGIC TREATMENTS												
AMITRIPTYLINE (Tryptanol)												
Repeated Measures												
HAM-D	Depression	2	23	32 – 39	mild	1.00*	none	Non-randomised	7.1	9	45	Saran, 1988; Dinan & Mobayed, 1992[b]
CITALOPRAM (Ciprimil) & CARBAMAZEPINE (Tegretol)												
Repeated Measures												
Clinical Impression Scale	Psychosocial	1	20	84	severe	.91	none	Non-randomised	6.7	4	48	Perino et al., 2001
Brief Psychiatric Scale	Psychosocial	1	20	84	severe	.60	none	Non-randomised	6.7	2	62	Perino et al., 2001
PHENELZINE (Nardil)												
Repeated Measures												
HAM-D	Depression	1	10	32	mild	.55	none	Non-randomised	7.2	2	62	Saran, 1988
CATECHOLAMINE TREATMENTS												
METHYLPHENIDATE (Ritalin)												
Independent Groups Repeated Measures												
KAS - Psychopathology	Psychosocial	1	38	116	severe	1.02	single	Randomised	8.3	4	45	Mooney & Haas, 1993
State Trait Anger Scale	Anger/Aggression	1	38	116	severe	.83	single	Randomised	8.3	3	53	Mooney & Haas, 1993

Cont'd

Table 2 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL %	Study Reference
KAS - Belligerence	Anger/Aggression	1	38	116	severe	.82	single	Randomised	8.3	3	53	Mooney & Haas, 1993
Profile of Mood States	Anger/Aggression	1	38	116	severe	.75	single	Randomised	8.3	3	53	Mooney & Haas, 1993
Organic Signs & Symptoms	Psychosocial	1	38	116	severe	.75	single	Randomised	8.3	3	53	Mooney & Haas, 1993
Working Memory Task	Memory	1	18	142	not specified	.51	double	Randomised	7.0	2	67	Kim et al., 2006
Cross-Over												
Distraction Task	Attention	1	19	74	mild/moderate/ severe	.56	double	Randomised	9.0	2	62	Whyte et al., 1997[1c]
APOMORPHINE (Apokyn)												
Repeated Measures												
Disability Rating Scale	Global outcome	1	7	10	severe	5.67	none	Non-randomised	8.0	27	2	Fridman et al., 2010[d]
Coma Near-Coma Scale	Arousal	1	7	10	severe	4.44	none	Non-randomised	8.0	21	2	Fridman et al., 2010[d]
QUETIAPINE (Seroquel)												
Repeated Measures												
Overt Aggression Scale-M	Anger/Aggression	1	7	99	mild/moderate/ severe	4.25	none	Non-randomised	6.1	20	4	Kim & Bijlani, 2001
Clinical Impression Scale	Psychosocial	1	7	99	mild/moderate/ severe	4.25	none	Non-randomised	6.1	20	4	Kim & Bijlani, 2001
NFI-Aggression	Anger/Aggression	1	7	99	mild/moderate/ severe	2.00	none	Non-randomised	6.1	9	19	Kim & Bijlani, 2001

Cont'd

Table 2 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL %	Study Reference
RBANS	Memory/Attention	1	7	99	mild/moderate/ severe	2.00	none	Non-randomised	6.1	9	19	Kim & Bijlani, 2001
ZIPRASIDONE (Geodon)												
Repeated Measures												
Agitated Behaviour Scale	Anger/Aggression	1	5	8	severe	3.07	none	Non-randomised	8.9	14	7	Noe et al., 2007
CHOLINERGIC TREATMENTS												
DONEPEZIL (Aricept)												
Independent Groups Repeated Measures												
PASAT	Attention	1	18	18	mild/moderate/ severe	2.93	double	Randomised	10.0	14	7	Zhang et al., 2004
Weschler Memory Scale-(original/III)	Memory	2	44	18 -21	mild/moderate/ severe or not specified	1.56*	double, not-reported	Randomised	10.0/6.5	15	27	Zhang et al., 2004; Kim et al., 2009
Boston Naming Test	Memory	1	26	21	not specified	1.56	not-reported	Randomised	6.5	7	27	Kim et al., 2009
Mini Mental State Exam	General cognition	1	26	21	not specified	1.27	not-reported	Randomised	6.5	5	35	Kim et al., 2009
Repeated Measures												
RAVLT	Memory	1	4	174	severe	1.59	none	Non-randomised	7.8	7	27	Masanic et al., 2001
Complex Figure Test	Memory/Perception	1	4	174	severe	.85	none	Non-randomised	7.8	3	48	Masanic et al., 2001
Rivermead Memory Test	Memory	1	4	174	severe	.61	none	Non-randomised	7.8	2	62	Masanic et al., 2001

Cont'd

Table 2 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL %	Study Reference
Memory Assessment Scale	Memory	1	10	63	mild/moderate/ severe	-.56	none	Non-randomised	6.4	2	62	Kaye et al., 2003
RAVMT	Memory	1	10	180	moderate/severe	.53	none	Non-randomised	8.9	2	67	Khateb et al., 2005
Reaction Time – Dual Task	Attention	1	10	180	moderate/severe	.50	none	Non-randomised	8.9	2	67	Khateb et al., 2005
SODIUM CHANNEL BLOCKERS												
CARBAMAZEPINE (Tegretol)												
Repeated Measures												
Shortened NFI	Psychosocial	1	10	58	severe	2.20	none	Non-randomised	8.1	10	16	Azouvi et al., 1999[e]
Global NFI	Psychosocial	1	10	58	severe	1.90	none	Non-randomised	8.1	9	21	Azouvi et al., 1999[e]
Agitated Behaviour Scale	Anger/Aggression	1	10	58	severe	1.01	none	Non-randomised	8.1	4	45	Azouvi et al., 1999[e]
PEPTIDE TREATMENTS												
LYSINE VASOPRESSIN (LVP)												
Repeated measures												
Weschler Memory Scale	Memory	1	26	256	severe	.62	none	Non-randomised	7.2	2	62	Eames & Wood, 1999

Cont'd

Table 2 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL %	Study Reference
PHOSPHOLIPID INTERMEDIATE												
CDP-CHOLINE (Citicholine)												
Independent Groups Repeated Measures												
Visual Retention Test	Memory	1	10	180	severe	.62	Not-reported	Randomised	4.8	2	62	Leon-Carrion et al., 2000
Lurias Memory Words	Memory	1	10	180	severe	.51	Not-reported	Randomised	4.8	2	67	Leon-Carrion et al., 2000

Note: $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to weighted effect size; Severity = range of injury severities contributing to combined effect size; M d_{wss} = mean effect size weighted by sample size; SD d_w = standard deviation of the weighted effect size; Min. d_w = minimum weighted effect size; Max. d_w = maximum weighted effect size; Nfs = Fail Safe N; OL% = percent overlap; Nfs = Fail Safe N; OL% = percent overlap; GDS = Gordon Diagnostic System; GOS = Glasgow Outcome Scale; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; NFI = Neurobehavioural Functioning Inventory; HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CRT = Choice Reaction Time; PASAT = Paced Auditory Serial Addition Test; RAVLT = Rey Auditory Verbal Learning Test; RAVMT = Rey Auditory Verbal Memory Test; KAS = Katz Adjustment Scale.

* HAM-D : SD = .04, Min = .97, Max = 1.03;

Weschler Memory Scale : SD = 1.53, Min = .67, Max = 2.84.

[1] Single group repeated cross-over design

Participants concurrently taking:

[b] temazepam for night sedation

[c] carbemazepine

[d] anti-epileptic and anti-spasticity drugs

[e] neuroleptics

The tricyclic antidepressant *desipramine* was the only serotonergic agent to be examined in a double-blinded study that used an independent groups repeated measures design. However, this treatment did not noticeably improve depressive symptoms (Affect/Mood Scale) after severe TBI (Wroblewski, et al., 1996) and, is therefore, only reported in Table 5.D of the Appendices. The remaining studies, all of which used an open-label repeated measures experimental design**,** showed moderate to very large improvements after mild TBI in clinician-rated depressive symptoms (HAM-D) with *amitriptyline* (Dinan & Mobayed, 1992; Saran, 1988) and *phenelzine* (Saran, 1988) (Table 2). In addition, combined treatment with *citalopram* and *carbamazepine* (open-label study) improved psychosocial functioning following a severe TBI (Perino, et al., 2001). These findings suggest that serotonergic agents may improve clinician-rated depressive symptoms following mild TBI (evidence based on treatment-aware clinicians) and psychosocial function after severe TBI but it is not possible to evaluate whether spontaneous recovery contributed to these results.

Catecholamine Treatments

There were a total of eight studies that examined five modulators of dopaminergic activity, including three that stimulate dopamine release (*methylphenidate, amantadine, apomorphine*) (Fridman, et al., 2010; Kim, Ko, Na, Park, & Kim, 2006; Kraus, et al., 2005; Mooney & Haas, 1993; Speech, et al., 1993; Whyte, et al., 1997) and two dopamine antagonists (*quetiapine, ziprasidone*) (Kim & Bijlani, 2006; Noe, Ferri, Trenor, & Chirivella, 2007), in blinded or open-label studies (see Table 5.B and 5.E of the Appendices). Two studies used an independent groups repeated measures design (Kim, et al., 2006; Mooney & Haas, 1993), two used a cross-over (Speech, et al., 1993; Whyte, et al., 1997), and four used a repeated measures design (Fridman, et al., 2010; Kim & Bijlani, 2006; Kraus, et al., 2005; Noe, et al., 2007). All studies used relatively small samples ($N \leq 38$). The inclusion criteria for one study permitted the concurrent use of carbemazepine (Whyte, et al., 1997) and another

allowed the concomitant use of anti-epileptic or anti-spasticity medication (Fridman, et al., 2010).

The dopamine and noradrenaline stimulant *methylphenidate* was examined by four studies (Kim, et al., 2006; Mooney & Haas, 1993; Speech, et al., 1993; Whyte, et al., 1997). Two of these used a randomised controlled independent groups repeated measures design (Table 2) (Kim, et al., 2006; Mooney & Haas, 1993). Sizeable reductions in anger and aggression (Katz Adjustment Scale [KAS], Belligerence subscale; State-Trait Anger Scale; Profile of Mood States) and an improvement in self- and relative-reports of psychosocial function (KAS, Psychopathology subscale; Organic Signs and Symptoms Inventory) were evident in a participant-blinded study after severe TBI (Mooney & Haas, 1993). With regard to cognition, memory (Working Memory Task) was found to improve in a single double-blinded study that used an independent groups repeated measures design, albeit with a smaller fail-safe N (Kim, et al., 2006). Attention (Distraction Task) also improved in one study that used a double-blinded cross-over design after a mild, moderate or severe TBI, although the fail-safe N was too small to draw any firm conclusions (Whyte, et al., 1997). There were no noticeable improvements in memory or attention in another cross-over design study after moderate to severe TBI (Table 5.E of the Appendices) (Speech, et al., 1993). While sample sizes were small, the fail-safe Ns calculated for the KAS Psychopathology and Belligerence subscales, State-Trait Anger Scale, Profile of Mood States, and the Organic Signs and Symptoms Inventory, make it unlikely that there would be findings in unpublished studies that would overturn these results.

In addition, one study investigated the dopaminergic agent *apomorphine* (Fridman, et al., 2010) and one investigated *amantadine* (Kraus, et al., 2005) in small samples that varied in injury severity. Both studies used an open-label repeated measures design. A very large improvement in global outcome (Disability Rating Scale) and arousal (Coma Near-Coma

Scale), together with very large fail-safe Ns, were found when *apomorphine* was used following severe TBI (Fridman, et al., 2010). There were no treatment benefits on any of the cognitive measures that were used to investigate *amantadine* (Appendices) (Kraus, et al., 2005).

Finally, open-label repeated measures designs were used to investigate the dopamine antagonists *quetiapine* (Kim & Bijlani, 2006) and *ziprasidone* (retrospective chart review) (Noe, et al., 2007) in very small samples (N < 10). Each treatment was investigated by a single study following mild, moderate or severe TBI. Both treatments resulted in very large improvements in anger and aggression (Modified Overt Aggression Scale; Neurobehavioural Functioning Inventory [NFI] Aggression subscale; Agitated Behaviour Scale) and very large fail-safe Ns. A marked improvement in psychosocial function (Clinical Impression Scale) and cognition (Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]), and a very large fail-safe N, was also found for *quetiapine* (Kim & Bijlani, 2006). However, *ziprasidone* (Noe, et al., 2007) was evaluated using a retrospective chart review, which may have affected the quality of the data that was available to the study authors.

Overall the findings suggest that specific dopaminergic treatments reduce combative behaviour (*methylphenidate, quetiapine, ziprasidone*) as well as improve memory and attention (*methylphenidate, quetiapine, apomorphine),* global outcome *(apomorphine)* and psychosocial function *(quetiapine)* following TBIs of varying severity. The results for *quetiapine*, *apomorphine* and *ziprasidone* (Fridman, et al., 2010; Kim & Bijlani, 2006; Noe, et al., 2007), were based on open-label studies and should, therefore, be interpreted with caution.

Cholinergic Treatments

Three cholinergic treatments were investigated by six studies: five studies examined *donepezil*, two using an independent groups repeated measures design (one double-blinded

(Zhang, et al., 2004), one did not report blinding (Kim, et al., 2009), and three using an open-label repeated measures design (Kaye, et al., 2003; Khateb, et al., 2005; Masanic, et al., 2001) (see Appendices Table 5.B and Table 5.F). The remaining study examined combined treatment with *physostigmine* and *lecithin* (Levin, et al., 1986) using a double-blinded independent groups repeated measures design. All six studies used small TBI samples (N = 4 - 26) of mild, moderate, severe or unspecified severity.

Treatment with *donepezil* resulted in very large improvements in objective assessments of attention (Paced Auditory Serial Addition Test [PASAT]) (Zhang, et al., 2004), memory (Wechsler Memory Scale [WMS]-III/original; Boston Naming Test) (Kim, et al., 2009; Zhang, et al., 2004), and general cognition (Mini Mental State Exam [MMSE]) (Kim, et al., 2009) using the most rigorous experimental design (Table 2). The large fail-safe Ns and small overlap between groups increases our confidence in this finding. Large to very large treatment benefits were also found for two other measures of memory (Rey Auditory Verbal Learning Test; Complex Figure Test) following a severe TBI (open-label repeated measures design) (Masanic, et al., 2001). However, a moderate decline in a single measure of memory (Memory Assessment Scale) was observed, albeit with a smaller fail-safe N, after mild, moderate and severe TBI in another open-label repeated measures study (see Appendices Table 5.F) (Kaye, et al., 2003).

In contrast, there were no noticeable improvements in cognition (memory, attention) after moderate to severe TBI following combined treatment with *physostigmine* and *lecithin* (Appendices) (Levin, et al., 1986). Together, the current findings suggest that *donepezil* improves memory and attention across a range of injury severities after TBI.

Sodium Channel Blockers (modulator of ion homeostasis)

A small single study (N = 10) used an open-label repeated measures design to assess the effects of treatment with the sodium channel blocker *carbamazepine* (Azouvi, et al., 1999)

following severe TBI (Appendices Table 5.B and Table 5.G). The concurrent use of neuroleptics was permitted in this study. Large to very large treatment benefits and large fail-safe Ns were found for two self- and relative-reports of psychosocial function (Shortened Neurobehavioural Rating Scale; Global Neurobehavioural Rating Scale) and one self- and relative-report measure of agitation (Agitated Behaviour Scale) (Table 2). This suggests that *carbamazepine* may be useful in improving behavioural symptoms following a severe TBI.

Peptide Treatments

There were three studies that investigated treatment with three peptides, all in small samples ($N \leq 26$) (see Table 5.B and Table 5.H of the Appendices). One study examined *lysine vasopressin* (Eames & Wood, 1999), one examined *cerebrolysin* (Alvarez, et al., 2008) and one examined *desmopressin* (Jenkins, et al., 1981), using an open-label repeated measures experimental design. Importantly, *lysine vasopressin* noticeably improved memory (Wechsler Memory Scale [WMS-original version]) following severe TBI (Table 2) (Eames & Wood, 1999), but neither *cerebrolysin* (Alvarez, et al., 2008) or *desmopressin* (Jenkins, et al., 1981) showed a noticeable improvement in cognition (see Appendices). Overall, this suggests that peptide treatments may improve some aspects of cognition following a severe TBI.

Phospholipid Intermediates

Lastly, the phospholipid intermediate *CDP-choline* (Leon-Carrion, et al., 2000) was investigated in a single study of 10 severe TBI patients using a non-blinded, randomised, and placebo-controlled, independent groups repeated measures experimental design (Table 5.B and Table 5.I of the Appendices). Moderate improvements were found for two memory measures (Benton Visual Retention Test; Lurias Memory Words) (Table 2), however, a small to moderate decline ($d = -.45$) was found for a single measure of attention (Sevilla's Computerised Neuropsychological Test Battery) (Appendices). Thus, following a severe

TBI, this treatment appears to provide objectively measured improvements in memory but may additionally impair attention.

Mixed time-to-treatment intervals

As indicated, when conducting this analysis it became apparent that a number of studies administered a pharmacological agent prior to, and spanning what we currently defined as the post-acute period (Range = 4 days to > 14 years) but after the acute period examined elsewhere (≤ 3days) (Wheaton, et al., 2009). Given the subjective nature of the cut-off that defined the post-acute stage (≥ 4 weeks post-injury), these studies were analysed separately. A total of seven studies fell into this category: two of which examined the serotonergic agents *sertraline* and *milnacipran*, three examined the dopaminergic treatments *methylphenidate* and *amantadine*, one examined the cholinergic treatment *donepezil*, and one examined the peptide *cerebrolysin* using an independent groups repeated measures, an independent groups, a repeated measures or a cross-over experimental design.

Serotonergic Treatments

Two serotonergic treatments were investigated in small samples following mild to moderate TBI (Kanetani, Kimura, & Endo, 2003; Lee, et al., 2005). The serotonin agonist *sertraline* was examined in a double-blinded study that used an independent groups repeated measures design (Lee, et al., 2005) (Table 3). When treatment was administered between two weeks and one year post-injury there was a noticeable increase in post-concussion symptoms and a marked decrease in psychomotor speed (Motor Speed – Choice Reaction Time [CRT]). Moderate declines were also found in general cognition, cognitive speed and memory. In contrast, there were moderate objectively measured improvements in selective attention (Wechsler Adult Intelligence Scale-Revised [WAIS-R] Digit Symbol) and in clinician-rated

Table 3: Treatments administered at mixed post-injury intervals with moderate to large effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL%	Study Reference
SEROTONERGIC TREATMENTS												
SERTRALINE (Zoloft)												
Independent Groups Repeated Measures												
Post Concussion Symptoms	Psychosocial	1	20	4	mild/moderate	-.86	double	Randomised	9.5	3	48	Lee et al., 2005 (Study 2)
Motor Speed – CRT	Psychomotor Speed	1	20	4	mild/moderate	-.81	double	Randomised	9.5	3	53	Lee et al., 2005 (Study 2)
Mental Arithmetic Test	General Cognition	1	20	4	mild/moderate	-.69	double	Randomised	9.5	3	57	Lee et al., 2005 (Study 2)
Choice Reaction Time	Cognitive Speed	1	20	4	mild/moderate	-.66	double	Randomised	9.5	2	57	Lee et al., 2005 (Study 2)
WAIS Digit Symbol	Attention	1	20	4	mild/moderate	.65	double	Randomised	9.5	2	57	Lee et al., 2005 (Study 2)
HAM-D	Depression	1	20	4	mild/moderate	.50	double	Randomised	9.5	2	67	Lee et al., 2005 (Study 2)
Memory Scanning Task	Memory	1	20	4	mild/moderate	-.50	double	Randomised	9.5	2	67	Lee et al., 2005 (Study 2)

Cont'd

Table 3 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL%	Study Reference
MILNACIPRAN (Ixel)												
Repeated Measures												
HAM-D	Depression	1	10	22	mild/moderate	1.85	none	Non-randomised	7.8	7	21	Kanetani et al., 2003
Mini-Mental State Exam	General Cognition	1	10	22	mild/moderate	1.20	none	Non-randomised	7.8	5	38	Kanetani et al., 2003
CATECHOLAMINE TREATMENTS												
METHYLPHENIDATE (Ritalin)												
Independent Groups Repeated Measures												
HAM-D	Depression	1	20	4	mild/moderate	1.59	double	Randomised	9.5	7	27	Lee et al., 2005 (Study 1)
Post Concussion Symptoms	Psychosocial	1	20	4	mild/moderate	.67	double	Randomised	9.5	2	57	Lee et al., 2005 (Study 1)
Quality of Life Scales	Psychosocial	1	20	4	mild/moderate	.61	double	Randomised	9.5	2	62	Lee et al., 2005 (Study 1)
BDI	Depression	1	20	4	mild/moderate	-.51	double	Randomised	9.5	2	67	Lee et al., 2005 (Study 1)

Cont'd

Table 3 Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Blinding (double, single, none)	Randomisation	Quality Score /10	Nfs	OL%	Study Reference
AMANTADINE (Symmetrel)												
Independent Groups Repeated Measures												
Disability Rating Scale	Global Outcome	1	35	4	moderate/severe	.83	double	Randomised	7.0	3	53	Meythaler et al., 2002
GOS (6 weeks)	Global Outcome	1	35	4	moderate/severe	.80	double	Randomised	7.0	3	53	Meythaler et al., 2002
PEPTIDE TREATMENTS												
CEREBROLYSIN												
Repeated Measures												
Syndrome Kurztest	Memory/Attention	1	20	81	mild/moderate/severe	1.54	none	Non-randomised	6.7	7	29	Alvarez et al., 2003[g]
GOS (1 month)	Global Outcome	1	20	81	mild/moderate/severe	.83	none	Non-randomised	6.7	3	53	Alvarez et al., 2003[g]

Note: $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to weighted effect size; Severity = range of injury severities contributing to combined effect size; M d_{wss} = mean effect size weighted by sample size; SD d_w = standard deviation of the weighted effect size; Min. d_w = minimum weighted effect size; Max. d_w = maximum weighted effect size; Nfs = Fail Safe N; OL% = percent overlap; Nfs = Fail Safe N; OL% = percent overlap; GDS = Gordon Diagnostic System; GOS = Glasgow Outcome Scale; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; NFI = Neurobehavioural Functioning Inventory; HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CRT = Choice Reaction Time; PASAT = Paced Auditory Serial Addition Test; RAVLT = Rey Auditory Verbal Learning Test; RAVMT = Rey Auditory Verbal Memory Test; NBI = Neurobehavioural Functioning Inventory; KAS = Katz Adjustment Scale.

Participants concurrently taking:[g] anticonvulsants

levels of depression (Hamilton Rating Scale for Depression [HAM-D]), albeit with smaller fail safe Ns. The serotonin and noradrenaline reuptake inhibitor *milnacipran* also reduced clinician-rated depressive symptoms (HAM-D) and improved general cognition on testing (Mini-Mental State Exam) in a single open-label study when individuals were treated from three weeks to more than one year after a mild to moderate TBI (Kanetani, et al., 2003). These findings suggest that serotonergic treatments administered prior to and across the post-acute period improve clinician-rated depressive symptoms but may increase post-concussion symptoms and reduce cognitive speed on more direct measures of speed of information processing after a mild to moderate TBI.

Catecholamine treatments

The dopamine stimulants *methylphenidate* and *amantadine* were examined by a further three studies; two of which investigated *methylphenidate* after mild, moderate or severe TBI using either a double-blinded independent groups repeated measures (Lee, et al., 2005) or cross-over design (Willmott & Ponsford, 2009). A marked improvement in a clinician-rated measure of depression (HAM-D) but not a self-report measure of depression (BDI) following mild to moderate TBI was found by one double-blinded study when treatment was given between two weeks and one year after injury (Table 3) (Lee, et al., 2005). In fact, there was a noticeable worsening of self-reported depressive symptoms. Improvements in psychosocial function (Post-Concussion Symptoms, Quality of Life Scale) were also evident, although with a smaller fail-safe N (Lee, et al., 2005). There were no improvements on any of the measures of attention that were used in a double-blinded cross-over design study that administered treatment from twelve days to more than one year after a moderate to severe TBI (See Appendices Table 5.E) (Willmott & Ponsford, 2009). In addition, when *amantadine* was administered between four days and six weeks after a moderate to severe TBI there were marked improvements in global outcome (Disability

Rating Scale, Glasgow Outcome Scale) in one double-blinded study that used an independent groups repeated measures design (Meythaler, et al., 2002).

Cholinergic treatments

Donepezil was examined in an open-label retrospective study using an independent groups design (Walker, et al., 2004) however, there was no improvement in psychosocial function (Functional Independence Measure) when treatment was administered between three and eighty-four days after entry to rehabilitation (see Table 5.F of the Appendices). Again the quality of data that is available for retrospective analysis may have influenced the results.

Peptide treatments

Finally, the peptide *cerebrolysin* was examined in a single open-label repeated measures design study. When this treatment was administered between three weeks to more than three years following a mild to severe TBI, marked improvements in memory, attention (Syndrome Kurztest) and global outcome (one month GOS) (Table 3) were evident (Alvarez, et al., 2003). The large fail-safe Ns increase the confidence that we can have in this finding.

Discussion

This study analysed data from 30 independent studies that investigated the cognitive and behavioural effects of 19 pharmacological treatments that were administered between four days and twenty years after sustaining a TBI. Twenty-three of these studies administered treatment between four weeks and twenty years after injury and seven administered treatment prior to four weeks and up to three years post-injury. The final data set included 395 participants with a TBI that were treated and 137 individuals with a TBI that served as non-treated controls, most of whom were moderate to severely injured males less than 40 years of

age. In total, seventy-three measures of cognitive and behavioural outcome were used, including 50 measures of cognition (memory, attention, executive function, general cognition, cognitive speed), four of mood (HAM-D; BDI), six of combativeness (anger/aggression), two of global outcome (GOS; DRS), 10 of psychosocial function (including those assessing quality of life and post-concussion symptoms), and one of motor speed (Choice Reaction Time).

For a pharmacological agent to be considered clinically useful following TBI, we decided that it must have measurable benefits to outcome (i.e., moderate to large treatment effects: $d_w \geq .5$) while allowing for the tendency for journals to publish studies with significant findings (N_{fs}). In addition, it is known that an *independent groups repeated measures* experimental design, followed by an *independent groups* design, control for more confounding variables and were therefore thought to provide stronger evidence of a treatment effect. When these criteria were applied to the results from this comparison, three treatments, that were each investigated using single- or double-blinded randomised controlled trials, produced noteworthy benefits and are discussed below.

Mood and Behaviour

With respect to *combative behaviour* (agitation, irritability, aggression), only the stimulant *methylphenidate* (Ritalin) showed adequate treatment benefits when participants were blinded to group allocation, as measured by the State-Trait Anger Scale (self-report), the KAS Belligerence subscale (relative report) and the Profile of Mood States (self-report) (Mooney & Haas, 1993). This supports both rodent studies and other human case reports which have found that increasing the availability of brain dopamine following TBI (methylphenidate, amantadine) reduces agitation and aggression (Chandler, et al., 1988; Chudasama, Nathwani, & Robbins, 2005; Granacher, 2008; Kikuchi, Nishino, & Ohyu, 2000;

Nickels, et al., 1994). Moreover, the fact that participants were blinded in terms of their group allocation reduces the impact of placebo effects on these results.

Psychosocial outcome (i.e. physical, psychological, social, and vocational outcome) was also investigated and was found to improve with *methylphenidate* (Ritalin) in all injury severities when participants were unaware of group assignment (Mooney & Haas, 1993). As treatment with methylphenidate is also associated with a reduction in depression and combativeness, both of which are correlated with an improvement in psychosocial function (McAllister, Flashman, Sparling, & Saykin, 2004), it is not known whether improved mood and reduced hostility contributed to this finding. However, it does appear that treatment with methylphenidate leads to improvements that have a broad impact on the psychosocial well-being of persons that have sustained a TBI. Again, the risk of placebo effects were minimised by blinding.

When those treatments that were administered prior to and across the post-acute period were also considered, two showed marked treatment benefits. In terms of *depression*, the stimulant *methylphenidate* (Ritalin) was the only treatment that markedly improved independent clinical ratings of depression (HAM-D) after mild to moderate TBI when both participants and assessors were blinded to group allocation (Lee, et al., 2005). Impaired cognition and fatigue are common symptoms of TBI that may have a negative impact on mood (Silver, et al., 2005). Improvements in arousal and attention and reductions in the levels of fatigue that are associated with dopaminergic treatments such as methylphenidate may, therefore, have contributed to improved mood (Gualtieri, 2002; High, Sander, Struchen, & Hart, 2005; Silver, et al., 2005). In addition, methylphenidate is thought to act by increasing brain concentrations of the neurotransmitters noradrenaline and serotonin which have antidepressant effects (Gualtieri, 2002; High, et al., 2005; Silver, et al., 2005). However, it is not yet clear whether these findings generalise to individuals who have sustained a more

severe TBI and who are likely to have greater neurochemical changes resulting from their injuries (Gordon, Haddad, Brown, Hibbard, & Sliwinski, 2000; High, et al., 2005).

Importantly, contradictory findings were observed for the different measures of depression. Specifically, *methylphenidate* was associated with increased levels of depression when self-reports of symptoms were used (BDI) (Lee, et al., 2005) compared to improvements in mood when clinicians who were blinded to group membership rated symptoms (HAM-D) (Lee, et al., 2005). This is consistent with other research which suggests that self-report measures of depression are less likely to show a treatment benefit than clinician ratings because the former ratings are affected by the cognitive (e.g., poorer memory and attention) and psychological (e.g., reduced insight, irritability and anxiety) disturbances that are associated with the TBI (Gordon, et al., 2000; Green, Felmingham, Baguley, Slewa-Younan, & Simpson, 2001; Rapoport, McCullagh, Shammi, & Feinstein, 2005; Rapoport, McCullagh, Streiner, & Feinstein, 2003). Moreover, self-report scales, such as the BDI, contain a number of somatic items (e.g., pain, fatigue) that may inflate depression scores (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Lezak, Howieson, & Loring, 2004). These factors may help explain the negative treatment effect that was found (Lee, et al., 2005) and suggests that clinician-rated measures of depression, or measures that do not contain somatic items (e.g., Hospital Anxiety and Depression Scale), may provide more appropriate assessments of depression in this context.

When *psychosocial outcome* was considered, the serotonin agonist *sertraline* had the undesired effect of increasing post-concussion symptoms after a mild to moderate TBI when both the participants and the assessors were blinded to group allocation (Lee, et al., 2005). Thus, if *sertraline* is used to treat depression, it is important to recognise that it may have the unwanted side-effect of increasing participant reports of other symptoms such as headache, irritability, and sleep disturbances. It may be that these symptoms are less well tolerated in

individuals with a TBI because of the other cognitive, psychological and physical challenges they face.

Finally, *global outcome*, as measured by the Glasgow Outcome Scale and Disability Rating Scale, improved in a double-blinded study with the dopamine stimulant *amantadine* (Symmetrel) following a severe TBI (Meythaler, et al., 2002). This supports other research, not analysed here, which has shown that minimising prolonged disruptions to dopamine following brain injury can improve functional recovery (Hornstein, Lennihan, Seliger, Lightman, & Schroeder, 1996; Kaelin, et al., 1996; Shiller, et al., 1999). In addition, a meta-analytic study found that orientation and arousal improved when amantadine was administered soon after injury suggesting that reducing both early and late disruptions to dopamine can improve outcome (Wheaton, et al., 2009). However, the beneficial effects that are found when a treatment is administered in the first few weeks after a TBI are likely to be affected by spontaneous recovery. Therefore, it is not clear whether these findings would translate to persons that are in the later stages of injury.

Cognition

One treatment, *donepezil*, resulted in large improvements in attention and memory (Paced Auditory Serial Addition Test, Wechsler Memory Scale) in one double-blinded study (Zhang, et al., 2004) and one study that did not report blinding (Kim, et al., 2009) following a mild to severe TBI or a TBI of unspecified severity. While combined treatment with *physostigmine* and *lecithin* (Levin, et al., 1986) did not show any sizeable treatment effects, the studies that evaluated these drugs used a number of different measures of varying difficulty (e.g., Continuous Performance Test, Digit Span, Trail Making Test, Digit Cancellation) to evaluate different aspects of cognition (sustained, divided, attention span, cognitive speed), which may have contributed to these null findings (see Table 5.F of the Appendices). Moreover as the Paced Auditory Serial Addition Test is a speed dependent task,

it is likely that this finding partly reflects an improvement in information processing speed (Lezak, et al., 2004).

With respect to *sertraline*, when treatment was initiated prior to and spanning the post-acute period, there were moderate to large negative treatment effects for psychomotor speed (Choice Reaction Time) and general cognition (Mental Arithmetic Test) when group allocation was blinded to both participants and the assessor (Lee, et al., 2005). This indicates that *sertraline* markedly impairs processing speed, as well as some aspects of cognition, following mild to moderate TBI. Again this finding may not generalise to individuals that are in the later stages of injury.

Other potentially beneficial treatments

A number of additional treatments may potentially benefit depressive symptoms (*sertraline, amitriptyline, milnaciparan, phenelzine*), combative behaviour (*quetiapine, ziprasidone, carbamazepine*), psychosocial outcome (*quetiapine, carbamazepine, combined treatment with citalopram and carbamazepine*), global outcome (*cerebrolysin, apomorphine*), and cognition (*milnacipran, quetiapine, apomorphine, cerebrolysin, lysine vasopressin*). However, these treatments were all investigated using a repeated measures experimental design, which confounds treatment effects with test practice effects (improved performance resulting from repeated testing on the same cognitive task) and spontaneous recovery (improved performance occurring as a part of natural recovery), thereby limiting the confidence that can be placed in these findings. In addition, as neither participants nor the assessor are blinded to group allocation in this experimental design, the additional confounds of participant expectation or assessor attitude may influence the study results. Only a blinded independent groups repeated measures experimental design controls for potentially important confounding variables (placebo effect, practice effects, spontaneous recovery, between group differences in baseline performance) and therefore, should be used in all future research.

Comparison with current clinical recommendations

There is currently little high quality evidence to support the effectiveness of pharmacological treatments in the management of cognitive and behavioural problems following TBI (Granacher, 2008; New Zealand Guidelines Group, 2006). Based on clinical recommendations and systematic reviews of the research literature, a range of treatments have previously been recommended for the treatment of cognitive and behavioural problems arising from TBI. These include methylphenidate, amantadine (Chew & Zafonte, 2009; New Zealand Guidelines Group, 2006; Waldron-Perrine, Hanks, & Perrine, 2008; Warden, et al., 2006) and donepezil (New Zealand Guidelines Group, 2006; Warden, et al., 2006) to improve attention and information processing speed; donepezil (New Zealand Guidelines Group, 2006; Warden, et al., 2006), methylphenidate (Waldron-Perrine, et al., 2008; Warden, et al., 2006) and CDP-choline (Warden, et al., 2006) for memory problems; methylphenidate (Warden, et al., 2006) and amantadine' (Waldron-Perrine, et al., 2008; Warden, et al., 2006) to improve general cognition; and brompcriptine (Waldron-Perrine, et al., 2008; Warden, et al., 2006) for executive function. In addition, the beta-blockers propranolol and pindolol (Fleminger, Greenwood, & Oliver, 2008; Waldron-Perrine, et al., 2008; Warden, et al., 2006), methylphenidate (Waldron-Perrine, et al., 2008; Warden, et al., 2006), sertraline (Waldron-Perrine, et al., 2008; Warden, et al., 2006), valproate (Fleminger, et al., 2008; Waldron-Perrine, et al., 2008), lithium (Chew & Zafonte, 2009; Waldron-Perrine, et al., 2008; Warden, et al., 2006) and amitriptyline (Warden, et al., 2006) have been recommended for the treatment of aggression, while depression is thought to benefit from the use of methylphenidate (Fleminger, et al., 2008), amantadine (Fleminger, et al., 2008), sertraline (Chew & Zafonte, 2009; New Zealand Guidelines Group, 2006; Waldron-Perrine, et al., 2008) and lamotrigine (Waldron-Perrine, et al., 2008). While, the current study provides quantitative data to support these recommendations for methylphenidate, donepezil, sertraline,

and CDP-choline, the strongest evidence is for the use of donepezil to treat cognitive problems (memory and attention) and methylphenidate to reduce behavioural disturbances (aggression and depression). Finally, this study extends current treatment recommendations by suggesting that (1) sertraline may lead to a decline in both motor function and cognition and an increase in the number of post-concussion symptoms reported by patients, (2) methylphenidate may also be used to improve psychosocial outcome and (3) amantadine may be beneficial to functional recovery.

Limitations of the current findings

There are a number of limitations to the current findings that warrant consideration. Firstly, the exclusion of non-English publications may have reduced the number of eligible studies. Moreover, some relevant studies may have been missed if the search terms were not included in the title, abstract or keywords. However, a large number of search terms were used and the bibliographies of all retrieved articles were searched in an effort to reduce the likelihood of this occurring. In addition, the calculation of a Fail-safe N assists in determining how many studies with null findings that were not captured by our analysis, whether due to publication bias or the inability to analyse non-English papers, are needed to call the findings into question.

Secondly, studies that failed to report data that could be converted into effect sizes reduced the pool of available data. This highlights the need for authors to routinely report basic summary data (means, standard deviations). A further twenty-five studies did not report all necessary data (Alvarez, et al., 2008; Alvarez, et al., 2003; Azouvi, et al., 1999; Dinan & Mobayed, 1992; Eames & Wood, 1999; Fridman, et al., 2010; Jenkins, et al., 1981; Kanetani, et al., 2003; Kaye, et al., 2003; Khateb, et al., 2005; Kim & Bijlani, 2006; Kim, et al., 2006; Kim, et al., 2009; Kraus, et al., 2005; Lee, et al., 2005; Leon-Carrion, et al., 2000; Levin, et al., 1986; Masanic, et al., 2001; Meythaler, et al., 2002; Mooney & Haas, 1993; Noe, et al.,

2007; Perino, et al., 2001; Saran, 1988; Wroblewski, et al., 1996; Zhang, et al., 2004) namely, a standard deviation for a difference score or a correlation between scores for those studies that used an independent groups repeated measures or repeated measures experimental design. While all available data for these studies was analysed, this limited the data that could be included. Moreover, many of the studies that were examined in this comparison were open-label (not blinded or participant-only blinding), which may have increased the treatment effects due to participant and assessor expectations (Hrobjartsson & Gotzsche, 2001; Schulz, et al., 1995). The random assignment of individuals to groups (treatment and placebo) and double-blinding (of both participants and assessors) would reduce this problem. Additionally, the findings from retrospective studies may be influenced by limitations in the quality and completeness of the data that was available for analysis (Dworkin, 1987; Gearing, et al., 2006).

Furthermore, injury severity data (GCS, PTA, LOC), level of education and time-to-treatment, were often not provided, thereby precluding a thorough critique of the studies. There was also considerable variation between studies with respect to the time post-injury that treatment was administered (i.e., between four weeks and twenty years post-injury for the post-acute period and 4 days to three years for studies of mixed injury interval), which may have impacted on the results. In addition, small samples ($N < 40$) were used to evaluate all of the drugs that were associated with sizeable treatment effects. While effect sizes calculate the magnitude of a treatment effect independent of sample size, the results are less reliable when based on small samples. Restricted sample sizes probably reflect both the difficulties associated with this type of research and the fact that such research is often opportunistic rather than being grant funded. Moreover, a large variety of different outcome measures were used to assess the relative efficacy of a treatment and, as a result, many findings were based on only a single study, which meant that most effect sizes could not be averaged across

studies. These treatments require additional investigation. In addition, while the current method of calculating a fail-safe N tends to yield lower values than some other methods (Rosenthal, 1979), the reported values are associated with a specific drug, experimental design and outcome measure. As there were limited studies that assessed the same drug, using the same experimental design and outcome measure, we believe that this method of calculating a fail-safe N provides a more appropriate and useful statistic for determining the number of additional studies that would be needed to reduce the obtained Cohen's *d* to a small treatment effect (*d* = .2). Finally, treatment benefits were often investigated in specific samples (i.e. mild, mild/moderate or severe TBI), leaving unanswered questions about whether these findings can be generalised to individuals who have sustained injuries that are more or less severe.

Conclusion

In the current analysis, four treatments were associated with moderate to large treatment effects (*sertraline*, *methylphenidate*, *donepezil*, *amantadine*). All were examined using a single- or double-blinded independent groups repeated measures, or an independent groups, experimental design, thereby increasing our confidence in these findings. Two treatments that were administered in the post-acute period met the study criteria for clinical usefulness ($d \geq .5$, large $N_{fs,}$). Specifically, *methylphenidate* reduced combativeness and also improved psychosocial outcome, and improvements in memory and attention were found with *donepezil*. In addition, marked treatment benefits were found for two agents that were administered prior to, and spanning the post-acute period, these being methylphenidate for depression, and *amantadine* for global outcome. Moreover, a meta-analysis of treatments administered prior to the post-acute period also showed an improvement in arousal with amantadine (Wheaton, et al., 2009), suggesting that dopaminergic agents may benefit different aspects of recovery across a wide time span. In contrast, early treatment with

sertraline worsened post-concussion symptoms and cognition, particularly psychomotor speed and general cognition, following mild to moderate TBI. While promising, these findings are based on single studies with small samples and require further evaluation using adequately powered randomised controlled trails to substantiate the conclusions that were drawn from this meta-analysis.

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Appendices

Table 5.A: Key search terms used in database searches

Figure 5.1: Details of electronic databse searches

Table 5.B: Demogrphic data, treatment and cognitive or behavioural test used for each study included in the meta-analysis

Table 5.C: Chemical group, pharmacological category and method of action of drugs

Appendix 5.A: Methodological quality rating system

Table 5.D: Serotonergic treatments: Weighted effect sizes for cognitive and behavioural measures

Table 5.E: Catecholamine treatments: Weighted effect sizes for cognitive and behavioural measures

Table 5.F: Cholinergic treatments: Weighted effect sizes for cognitive and behavioural measures

Table 5.G: Sodum channel blockers (modulators of ion homeostasis): Weighted effect sizes for cognitive and behavioural measures

Table 5.H: Peptide treatments: Weighted effect sizes for cognitive and behavioural measures

Table 5.I: Phospholipid intermediates: Weighted effect sizes for cognitive and behavioural measures

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Chapter 6: Discussion

Three meta-analyses were undertaken to evaluate the experimental and clinical research that has investigated the impact of pharmacological treatments on outcome in adult rodents and humans following TBI. Each study met all but one of the recommendations set out in the PRISMA Statement for the reporting of meta-analyses (Liberati, et al., 2009), this being the inclusion of additional sub-group analyses. However, the small number of studies that examined the same treatment, using the same experimental design and measure precluded this type of analysis. The current discussion outlines the main findings of each study, followed by a comparison of the results from Study 1 and Study 2, which examined the impact of early treatments in rodents and humans, and those of Study 2 and Study 3, which examined early and post-acute treatments in clinical settings. Limitations to the current research will then be presented, followed by suggestions for future research.

Summary of the Main Findings

The first study (Chapter 3) assessed the impact of treatments (≤ 1 week post-injury) on cognitive, behavioural and motor outcome in adult male rodents following experimentally induced TBI. Sixty of the 91 treatments that were analysed improved outcome and four reduced performance, suggesting that the treatments were generally efficacious in this group. The specific treatments that were efficacious in *either* animal or human studies are summarised in Table 1. Full details of all of the treatments that were examined in the animal and human studies can be found in Appendix 6.A. Overall, anti-inflammatories showed the greatest benefit to cognition and motor function as evidenced by the large number of positive trials. Improvements were also more likely to be found on the most frequently used measures of outcome, namely; the Morris Water Maze, the Composite Neuroscore and the Neurological Severity Score, and when treatment was administered at higher dosages within an hour of injury.

Table 1: Summary of treatments that showed efficacy in *either* animal or human studies.

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
Serotonergic			
8-OH-DPAT	.80		
Amitriptyline			1.00
Citalopram + Carbemazepine			.60 - .91[1]
Phenelzine			.55
Sertraline			-.86 - .65[1]
Milnacipran			1.20 – 1.85[1]
Catecholamines			
Rasagline	2.02		
Haloperidol	-1.49		
Methylphenidate	1.48		-.51 – 1.59[1]
L-Deprenyl	1.01		-
Apomorphine	-		4.44 – 5.67[1]
Ziprasidone			3.07
Quetiapine			2.00 – 4.25[1]
Amantadine		1.86	.80 - .83[1]
Cholinergic			
LU 25-109-T	1.27		
ENA 713 + Scopolamine	-1.23		
ENA 713	.88 – 2.40[1]		
Scopolamine	.82		
Donepezil			-.56 – 2.93[1]
Modulators of Ion Homeostasis			
Calcium			
SNX – 185	.85 – 2.17[1]		
Ziconotide	1.17 – 1.70[1]		
Sodium			
Carbemazepine			1.01 2.20[1]
Thyrotropin-Releasing Hormone Analogues			
TRH 35b	5.70		
YM 14673	1.43		
YM 14673 + Nalmefene	1.33		
2-ARA-53a	.93		
Vasodilators			
SB 209670	1.94		
SB 234551	1.56		
Opioids			
Nalmefene + Dextrorphan	1.25		
Anti-inflammatories			
B3	.91 – 4.09[1]		
VCP	2.37 – 3.56[1]		
Simvastatin	2.49		
Atorvastatin	1.41 – 2.43[1]		
C1-INH	.90 – 1.30[1]		
Minocycline HCl	1.03		
IL-18BP	1.00		
COG 1410	.95		
CP-0127		6.07	

Cont'd

Table 1 Cont'd

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
Immunosuppressants			
Cyclosporin A	3.02		
Modulators of Free Radical Formation			
Bemithyl	1.00 – 16.49[1]		
DETA/NONOate	2.53 – 3.40[1]		
CDP-Choline	.97 – 1.76[1]		.51 - .62[1]
PBN	1.66		
B2	1.14 – 1.60[1]		
DMSO	1.27		
Murine IgG	1.23		
Anti-ICAM	1.19		
L-NIL	1.19		
Inosine	1.15		
1400W	.98		
Steroids			
Raloxifene	1.14		
Modulators of Amino Acid Activity			
MgCl + B2	15.64		
MgSO	1.14 – 1.81[1]		
CP-98,113	.94 – 1.66[1]		
HU-211 (Dexanabinol)	1.53 – 1.60[1]	-	
MgCl	1.03 – 1.43[1]		
½MgCl + ½B2	1.24		
Dextrorphan	1.20		
CP-101,606	1.07	-	
CP-101,581	1.04		
DCS	.87 – 1.03[1]		
Aniracetam	.91		
Eliprodil	.88		
Growth Factors			
EPO + BrdU	2.38		
EPO	.97 – 1.41[1]		
NGF	1.07		
Other			
Pyracetam	1.07 – 8.41[1]		
FDP + DMSO	4.78		
NIM 811	3.85		
FTS	.88 – 2.28[1]		
GTSs	-1.91		
Fenofibrate	1.50		
HSA	1.47		
sAPPa	-1.02		
INO-1001	.93		
FDP	.86		
Lysine Vasopressin			.62
Cerebrolysin			.83 – 1.54[1]
Total Treatments	64	2	15

Note: - = treatment examined but not efficacious in this group

[1] Indicates the range of large (rodent) or moderate to large (human) effect sizes for different outcome measures

Study 2 (Chapter 4) attempted to extend the findings of Study 1 by examining the efficacy of pharmacological treatments administered acutely (≤ 3 days post-injury) to adult humans. Acute treatments are designed to alter the secondary cascade of events, thereby limiting additional damage to the brain and improving outcome following TBI (Cawley, et al., 1998; Tolias & Bullock, 2004). There were far fewer treatments examined in this context than in the previous animal study, with only two of the eleven treatments that were analysed improving the level of arousal (Glasgow Coma Scale) in a clinical population, namely; the dopamine agonist and NMDA receptor antagonist, amantadine, and the bradykinin B2 antagonist and anti-inflammatory, CP-0127 (Bradycor) (refer to Table 1 and Appendix 6.A). Although injury-to-treatment interval did not appear to influence outcome, drug dosage showed differential effects on the Glasgow Outcome Scale for three treatments (dexanabinol, LF 16-0687 Ms [Anatibant], GK-11 [Gacylidine]).

The final study, outlined in Chapter 5, extended the findings of the second study by investigating the effectiveness of treatments administered to adults in the post-acute period (≥ 4 weeks post-injury). Treatments that are administered in the late stages of an injury act by compensating for persistent biochemical changes that are associated with cognitive and behavioural problems following TBI (Fann, et al., 2000; Khateb, et al., 2005; Masanic, et al., 2001). As Table 1 shows, many of the treatments that were analysed in the third study improved clinical outcome, with catecholamines and the cholinergic agent, donepezil, being the most beneficial. Three agents (sertraline, methylphenidate, donepezil) showed mixed findings (positive and negative) on different outcome measures, suggesting that the measure that is used to evaluate outcome influences the probability of finding a treatment benefit.

6.1 Translation between animal and human research

There were only two treatments that were analysed acutely in both animals (Chapter 3) and humans (Chapter 4), namely; the modulators of amino acid activity, HU-211 and CP-

101,606 (Table 2 summarises efficacious treatments that were examined in *both* animals and humans or acute and post-acute treatment studies). These treatments improved outcome in rodents when administered within six hours of a focal (weight drop) or diffuse TBI (lateral fluid percussion) but did not improve outcome in humans when administered between six and eight hours after a severe injury. While this appears to suggest that treatment benefits failed to translate from animals to humans, the animal studies involved a moderate or unspecified level of injury severity. It is, therefore, possible that this treatment may not be effective for a more severe injury, and consequently greater damage to the brain, or in humans (Schonberger, Ponsford, Reutens, Beare, & O'Sullivan, 2009). Moreover, humans were administered treatment later and at much lower dosages than rodents, taking into account body weight, and this may have reduced the efficacy of these treatments.

There are also a number of other factors that may have contributed to the disparity between the rodent and human research findings. Firstly, anatomical differences between rodent and human brains, including the smaller size, mass and poorly defined sulci of the rodent brain, makes rodents less vulnerable to the acceleration/deceleration and rotational forces that cause axonal injury, concussion, and poorer outcome in a clinical population (Cernak, 2005; Finnie, 2001; Park, Fernandez, Dujovny, & Diaz, 1999). Moreover, while clinical trials often include persons with severe TBIs, rodents tend to be injured at the lower mild or moderate levels of severity, partly because even small incremental increases in the injury load can be fatal to rodents (Park, et al., 1999). This is why few of the experimental studies that were analysed examined severely injured animals.

Table 2: Summary of efficacious treatments that were examined in *both* animals and humans or acute and post-acute treatment studies.

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
Catecholamines			
Methylphenidate	√		√
Apormorphine	-		√
Amantadine		√	√
Modulators of Free Radical Formation			
CDP-Choline	√		√
Modulators of Amino Acid Activity			
HU-211	√	-	
CP-101,606	√	-	

Note : √ = efficacious treatment; - = treatment examined but not efficacious in this group.

The heterogeneity of human TBI may also impact on treatment efficacy. Specifically, experimental models deliver highly controlled and replicable injuries to specific brain regions resulting in a well-defined set of cognitive, behavioural and motor problems (Tolias & Bullock, 2004). In comparison, clinical populations sustain TBIs from various causes (e.g. motor vehicle accidents, falls, assaults) and at different levels of force, leading to individual variation in the degree and location of the brain injury, and the type and complexity of the cognitive and behavioural problems that occur (Morales, et al., 2005; Sudarsanan, Chaudhary, Pawar, & Srivastava, 2006). In additon, human TBIs may be accompanied by comorbid physical injuries, not captured in experimental models, which can further complicate the recovery process (Greenwald & Rigg, 2009).

The condition of the brain at the time of injury, as well as premorbid characteristics (e.g., age, education, personality), could also explain variability in outcome between experimental and clinical populations. For example, experimental research typically uses a highly homogenous group of healthy young rodents of a single strain and gender (Tolias & Bullock, 2004). In contrast, up to 50% of persons that sustain a TBI are affected by pre-injury drug and alcohol use, which may increase the risk of mortality and delay the recovery process (Martelli, Bender, Nicholson, & Zasler, 2002; Parry-Jones, Vaughan, & Miles Cox, 2006; Rao & Lyketsos, 2000). Premorbid personality and behavioural traits may also be exaggerated after TBI as a result of the injury itself, or emotional stresses that are associated with the traumatic event (Greenwald & Rigg, 2009). In addition, increasing age, male gender, a lower level of social class and education, and learning problems have been linked to poorer outcome in humans (Deb, Lyons, Koutzoukis, Ali, & McCarthy, 1999; Rao & Lyketsos, 2000; Sudarsanan, et al., 2006). Each of these factors could influence the degree of clinical improvement that is possible (Ponsford, et al., 2000; Sudarsanan, et al., 2006).

With respect to the other treatments that were examined, the remaining nine drugs that were administered acutely to humans were not analysed in animals, precluding a between-group comparison of their efficacy. Of these nine, only two treatments (CP-0127, amantadine) improved outcome in a clinical population. The absence of preclinical data for the remaining seven treatments may, in some instances, indicate that these drugs were tested or developed for use in other clinical populations (e.g., persons with cardiovascular disorders, diabetes, or influenza) that do not replicate the full range of secondary injuries associated with TBI. This may partly explain why these treatments were not efficacious.

As only a small number of the treatments that were analysed in rodents were also investigated in humans, different treatments that targeted the same mechanism of injury were also compared. This comparison indicated that anti-inflammatory treatments benefited both

rodents and humans when treatment was administered soon after a TBI. Specifically, the first meta-analysis concluded that four anti-inflammatory treatments (simvastatin, atorvastatin, C1-INH, and B3) reduced cognitive and motor problems in adult rodents, while the bradykinin B2 antagonist, CP-0127 (Bradycor), and the dopamine agonist and NMDA antagonist, amantadine, improved arousal (GCS) in humans. This suggests that treatments that reduce inflammation and an associated rise in intracranial pressure may improve early outcome in both groups. However, it is also important to recognise that the anti-inflammatory treatments that were investigated in animals targeted different biochemical changes and/or receptors in the brain than those that were investigated in humans. As a result, it remains unclear whether treatment benefits would translate between these groups if comparisons were made on the basis of a specific anti-inflammatory agent.

In addition, anti-inflammatories (CP-0127 [Bradycor], methylprednisolone, dexanabinol) did not, in general, improve long-term outcome (GOS) in humans, suggesting that initial improvements may not lead to ongoing benefits in a clinical population and, in the case of methylprednisolone, may have a detrimental effect on recovery. This may be partly explained by considering the opposing roles of the inflammatory response to TBI (Frugier, et al., 2010), whereby the release of pro- and anti-inflammatory cytokines may encourage inflammation or promote neural regeneration and repair (Chen, et al., 2008; Frugier, et al., 2010; Lenzlinger, et al., 2001; Morganti-Kossman, et al., 1997; Csuka, et al., 1999; Morganti-Kossmann, et al., 1999). It is therefore possible that, when given acutely, some anti-inflammatories may improve early outcome by reducing brain swelling, intracanial pressure and neural damage, while simultaneously inhibiting the initiation of natural regenerative processes that are important for long-term recovery.

To summarise, the first two studies of this thesis suggest that reducing inflammation improves initial impairments in cognition and motor function in rodents and arousal in

humans. Adult humans also showed an improvement in arousal with the dopamine stimulant amantadine. However, the early benefits associated with anti-inflammatory agents do not appear to translate to long-term improvements in a clinical population.

6.2 Translation between early and post-acute treatment

Two of the nineteen treatments that were analysed in humans in the post-acute period (amantadine, desmopressin), were also analysed in the acute stage post-injury, however, only amantadine was efficacious (see Table 2 for a summary of efficacious treatments that were examined in *both* animals and humans or acute and post-acute treatment studies). Moreover, amantadine improved both early arousal and long-term outcome (GOS, Disability Rating Scale) following injury, suggesting that this treatment may play an important role in minimising the acute and persistent disruptions to dopamine in the brain that are associated with poorer outcome after TBI (Bales, et al., 2009; Schneider, et al., 1999). The catecholamine transport inhibitor methylphenidate also improved outcome across a wide time-span (e.g., reduced combativeness and depressive symptoms, improved psychosocial outcome), further supporting a role for dopaminergic neurotransmission in early and late recovery of function after injury (Chandler, et al., 1988; Kline, Yu, et al., 2002; Lee, et al., 2005; Saniova, et al., 2004).

Although the current results support the role of dopamine disruptions in the development of cognitive and behavioural problems following TBI (Fridman, et al., 2010; Meythaler, et al., 2002; Sawyer, Mauro, & Ohlinger, 2008; Wagner, et al., 2009), dopamine release is not the only method by which amantadine acts on the brain. Specifically, this treatment also acts as a mild NMDA antagonist (Blanpied, Clarke, & Johnson, 2005) and anticholinergic agent (Nastuk, Su, & Doubilet, 1976). Traumatic brain injury results in a complicated interaction between a number of secondary biochemical events, therefore, it

could be argued that the benefits associated with this treatment result from its actions on multiple biochemical alterations, rather than a single event (Blanpied, et al., 2005; Novack, et al., 1996; Tsai, Mansour, Eldefrawi, Eldefrawi, & Albuquerque, 1978).

A number of methodological differences may have also influenced the likelihood of finding an improvement in both the early and late treatment groups. Firstly, drug dosages varied, with acute amantadine treatment administered at a dosage of 400 mg/day and late treatment at a dosage of 200 mg/day, suggesting that higher doses of this drug are required to produce early treatment benefits. However, as injury severity also differed, it is possible that less severely injured individuals required a lower dose of this drug for improvement. In addition, while early treatment with anti-inflammatories did not result in enduring benefits to outcome, the long-term benefits of acute amantadine treatment were not evaluated. As a result, it is unclear whether the beneficial effects of early treatment with amantadine would have been sustained over time.

The seventeen remaining drugs that were examined in the post-acute period were not analysed in humans during the acute stage post-injury. However, it is important to note that treatments that are administered acutely are designed to reduce secondary biochemical disruptions, whereas late treatments compensate for persistent biochemical changes (Khateb, et al., 2005; Tolias & Bullock, 2004). Therefore, only treatments that target changes know to be affected in the post-acute stage, or those that have shown efficacy in clinical populations with similar biochemical disturbances (e.g. dementia, Parkinson's disease), may have been selected for investigation. In addition, three treatments that were examined post-acutely in humans were also examined in rodents, two of which showed efficacy in both groups, namely; the catecholamine, methylphenidate, and the modulator of free radical formation, CDP-choline. While this suggests that some of the treatments that address secondary damage in animals may also benefit later outcome in humans, animal research does not currently

investigate the long-term benefits of treatment, thereby precluding a direct comparison of these findings.

In summary, the second and third studies suggest that stimulating both early and persistent disruptions to dopamine release following human TBI improves arousal as well as cognition and behaviour. However, it remains unclear whether the beneficial effects of early treatment can be maintained over time, or if injury severity and drug dosage contributed to these improvements.

6.3 Limitations

The limitations associated with each of the individual studies were presented in the relevant Chapters (Chapters 3, 4 and 5). The following discussion therefore focuses on potential limitations in the translation of research between studies.

Firstly, it could be argued that setting a higher standard of treatment efficacy for the experimental research in comparison to the human research may have reduced the number of treatments that were available for comparison against the human cohort. However, it was considered important to identify only the most efficacious treatments with the strongest evidence-base for possible evaluation in a human TBI group. This was, in part, due to the time and costs that are associated with conducting treatment trials, as evidenced by the small number of large-scale randomised controlled trials that were identified (Kraemer, Wilson, Fairburn, & Agras, 2002; Tolias & Bullock, 2004; Van der Worp, et al., 2010).

Secondly, when comparing the animal and human literature early treatment benefits were only evident when a comparison was made on the basis of chemical group rather than a specific treatment. While this provides a rational for administering treatments that target the same secondary event (e.g. inflammation), the method by which these treatments reduce secondary injury differ (Blanpied, et al., 2005; Hoane, et al., 2006; Lu, et al., 2007; Narotam,

et al., 1998). It is therefore uncertain whether the experimental treatments that were analysed here would be efficacious in a clinical population.

Thirdly, only the data from studies that used adult male rodents were analysed in Study 1, whereas in Studies 2 and 3 clinical efficacy was investigated in both adult males and females. While it is important to ensure that experimental trials are reproducible and extraneous variables that may influence treatment efficacy are considered, both rodent (O'Connor, et al., 2003) and human research suggest that there are sex differences in oedema formation and outcome following TBI (Liossi & Wood, 2009; O'Connor, Cernak, & Vink, 2006; Yurkewicz, et al., 2005). The exclusion of females from animal research may therefore limit the translation of these findings to humans and, consequently, the strength of evidence for their use in a human TBI population (Tolias & Bullock, 2004).

Finally, a number of methodological variables may have impacted on treatment efficacy. These include differences in injury severity, and the experimental design that is used to evaluate a treatment (Filipova, et al., 1989; Lepeintre, et al., 2004; Morris & DeShon, 2002; Yurkewicz, et al., 2005). Studies that are of a high quality and those that include both randomisation and blinding may also provide better evidence of a treatment effect. However, as few studies used the same treatment and measure to assess outcome, only small numbers of studies could be combined, limiting the statistical analysis of this information. This may reduce the extent to which the current findings can be generalised between studies and to persons with TBIs that differ in severity. Therefore, only the strongest evidence for treatment efficacy has been presented and, where possible, the potential impact of these variables has been identified.

6.4 Future directions for research

The current findings have expanded on current research in the area of pharmacology and TBI, and detected a number of potential considerations for future research in this field.

Firstly, this research has shown that reducing inflammation, oedema and intracranial pressure in the early stages of a TBI effectively improves outcome in both rodents and humans. This has important implications for future research by suggesting that treatment benefits translate from an experimental to a clinical population. However, it is evident from these findings that not all anti-inflammatory treatments are beneficial to outcome in humans and indeed some may have an adverse impact on long-term recovery (e.g. methylprednisolone) (Kreutzberg, 1996; Sloka & Stefanelli, 2005). This highlights the importance of identifying the method of action of the drug that is being examined and its impact on the brain, prior to assessing its efficacy in a clinical population.

It has also been concluded that the dopamine agonist amantadine improves early outcome in a clinical population. This improvement may partly result from its relatively weak antagonism of NMDA receptors, thereby reducing the excessive release of excitatory amino acids, which contribute to cellular death following TBI (Choi, et al., 1987). However, as none of the other NMDA antagonists that were investigated in humans showed an improvement in outcome and, indeed, one showed a detrimental effect on recovery, it is likely that enhancing dopamine release is an important contributor to these treatment benefits. Moreover, amantadine and dopaminergic treatments in general improved outcome in the post-acute stage after injury, suggesting that increasing the availability of dopamine in the brain following TBI benefits both early and persistent cognitive and behavioural problems. However, these findings were based on single studies and therefore require further empirical evaluation.

Finally, the current findings suggest that a number of factors may influence the translation of experimental research to a clinical population. In particular, most of the experimental literature minimises gender differences in the response to a TBI by including only male rodents (O'Connor, et al., 2003, 2006). However, the exclusion of intact females

may limit the degree of support that this research provides for the treatment of human TBI. Intact females should therefore be included in future experimental research to address this issue. Moreover, there are few, if any, experimental studies that have evaluated late treatment or long-term treatment benefits following TBI. As a result, animal research bears little relationship to the treatment of long-term outcome in a clinical population. An examination of the benefits of late treatments following experimental TBI may provide important information for clinical use.

6.5 Conclusions

In conclusion, this thesis found that anti-inflammatory treatments administered soon after a TBI improved early outcome but not long-term recovery in rodents and humans. However, not all anti-inflammatory treatments improved outcome in a clinical population, possibly due to differences in the method of action of the drugs. In addition, stimulating dopamine release improves both early arousal and long-term outcome in adult humans, although higher dosages may be required at earlier time points or following severe injuries to produce treatment benefits. These findings highlight the need for experimental studies to include a variety of injury severity levels (mild, moderate, and severe) and types of TBI injury (focal and diffuse), later injury-to-treatment intervals (> 1 hour post-injury), and testing periods (long-term outcome), and both males and females in their research in order to more accurately reflect the attributes of a clinical population and improve the strength of evidence for the use of pharmacological treatments. It is also evident that randomised controlled trials provide the best evidence of a treatment effect and these should be used in any future research.

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Appendices

Chapter 3

Figure 3.1: Secondary Injury Cascade

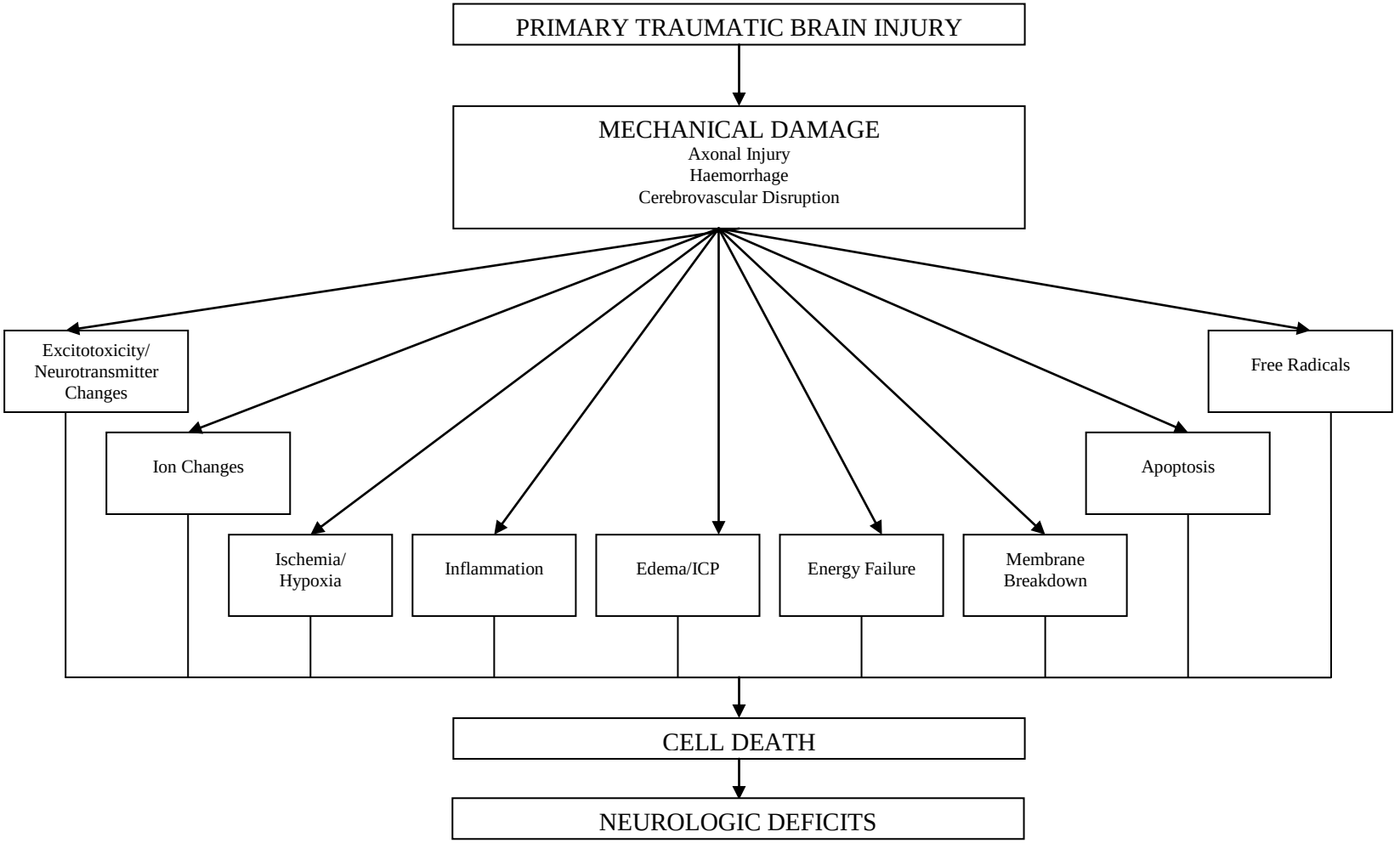

Figure 3.2: Details of electronic database searches

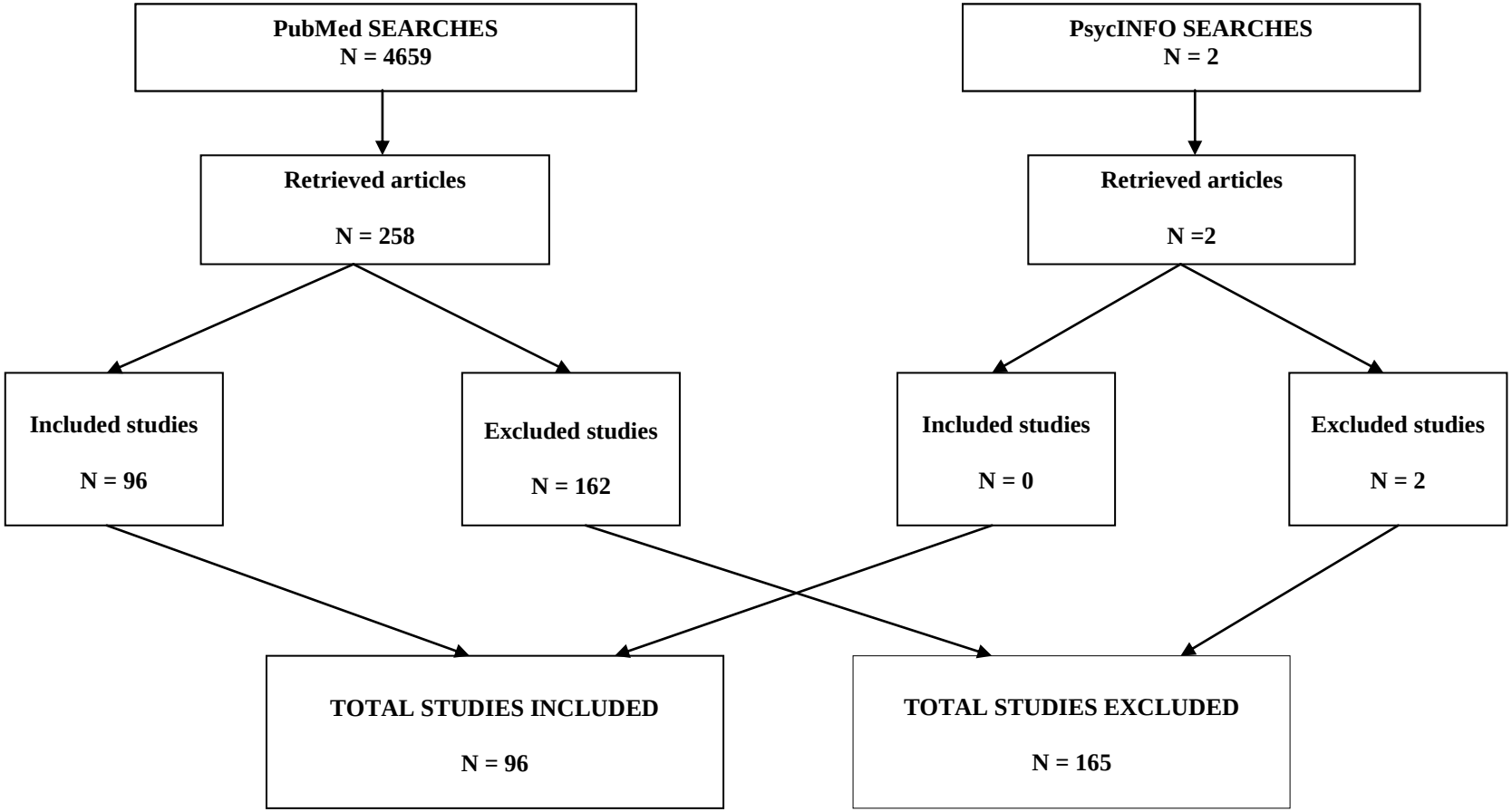

Table 3.A: Separation of studies using different animals for each treatment condition

Author	**Drug(s)**	**Rationale**	**Total $N_{Studies}$**
Louin, Marchand-Verrecchia et al (2006)	AG, L-NIL, 1400W 1400W	Three drugs Two treatment protocols	4
Erlich, Alexandrovich et al (2007)	Rapamycin	Two drug dosages	2
Lu, Qu, Goussev et al (2007)	Atorvastatin Simvastatin	Two experiments with different time-to- testing Two drugs	3
Baranova, Whiting, Hamm (2006)	Aniracetam	Two drug dosages	2
Hoane, et al (2006)	B3	Two drug dosages	2
Hoane, Tan, Pierce et al (2007)	COG 1410	Two drug dosages	2
Zarubina (2003)	Bemithyl Piracetam	Two drugs	2
Panikashvili, Simeonidou et al (2001)	2-AG	Three drug dosages	3
Dempsey, Rao (2003)	CDP-Choline	Three drug dosages	3
Barbre, Hoane (2006)	MgCl2 B2	Two drugs One drug combination with two different dosages	4

Cont'd

Table 3.A Cont'd

Author	**Drug(s)**	**Rationale**	**Total $N_{Studies}$**
Browne, Leoni et al (2004)	NPS 1506 MgSO4	Two drugs	2
Lee, Galo, Lyeth et al (2004)	SNX-185	Three drug dosages	3
Wang, Gao, et al (2006)	Levetiracetam	Two drug dosages	2
Barone, Ohlstein et al (2000)	SB234551 SB209670	Two drugs: One with two different dosages One with four different dosages	6
Besson, Chen et al (2005)	Fenofibrate	Two drug dosages	2
Chen, Shohami et al (1998)	ENA713	Three drug dosages Two drug dosages with different time-to- treatment intervals	13
	Scopolamine Mecamylamine	Two drug dosages One drug dosage One drug combination with two different dosages One drug combination with different dosages	
Chen, Shohami, Constantini et al (1998)	Rivastigmine Mecamylamine Scopolamine	Two drug dosages One single dose One single dose One drug combination One drug combination with two different dosages	7

Cont'd

Table 3.A Cont'd

Author	Drug(s)	Rationale	Total $N_{Studies}$
Cheney, Weisser et al (2001)	BMS 204352	Two drug dosages	2
Chong, Feng (2000)	NBP	Three drug dosages	3
de la Torre (1995)	FDP DMSO	Two drugs One drug combination	3
Faden (1993)	YM14673 Nalmefene Dextrorphan	Three drugs Two different drug combinations	5
Goss, Hoffman, Stein (2003)	Progesterone	Three drug dosages	3
Hall, Kupina, Althaus (1999)	PenME	Four drug dosages	4
Hayashi, Shimada et al (1994)	Nizofenone	Three drug dosages	3
Holloway, Harvey et al (2007)	Lactate	Four drug dosages	4
Huang, Chen et al (1999)	Rasagiline Scopolamine	One drug One drug combination	2
Ji, Kim, Park et al (2005)	GTSs	Two drug dosages	2
Knoblach, Faden (2002)	Anti-ICAM-1 IgG	Two drugs	2
Lu, Qu, Goussev, Jiang (2007)	Atorvastatin Simvastatin	Two drugs	2

Cont'd

Table 3.A Cont'd

Author	**Drug(s)**	**Rationale**	**Total $N_{Studies}$**
Lyeth, Ray et al (1992)	Scopolamine	Three different time-to-treatment intervals	3
Marklund et al (2001)	PBN	Two drugs	2
	S-PBN		
Mesenge, Margaill et al (1998)	Melatonin	Two different groups of animals with same dosage and time-to-treatment interval	13
	PBN	Two different groups of animals with same dosage and different times-to-treatment intervals	
		Two different groups of animals with different drug dosages	
		Four different groups of animals with same dosage	
		Three different groups of animals with different dosages	
Mesenge, Verrecchia et al (1996)	L-NAME	Two drugs and two time-to-treatment intervals with same dose of single drug	3
	7-NI		
O'Dell, Hamm (1995)	MDL 26,479	Two drug dosages	2
Okiyama, Smith, White et al (1997)	CP 101,606	Three drugs	3
	CP 101,581		
	CP 98,113		
Pike, Hamm (1997)	LU 25-109-T	Two drug dosages	2

Cont'd

Table 3.A Cont'd

Author	Drug(s)	Rationale	Total $N_{Studies}$
Pike, Hamm, Temple et al (1997)	THA	Three drug dosages	3
Shohami, Novikov, Bass (1995)	HU-211	Three times-to treatment intervals	3
Tang, Noda Nabeshima (1997b)	SCH-23390 Sulpiride	Two drugs with two different drug dosages One drug combination with two different drug dosages	6
Tang, Noda, Hasegawa, Nabeshima (1997a)	VA-045	Four drug dosages	4
Tang, Noda , Hasegawa, Nabeshima (1997b)	VA045	Two experiments with four drug dosages in each	8
Tang, Noda, Nabeshima (1997a)	Apomorphine Haloperidol SCH 23390 Sulpiride	Four drugs each with three different drug dosages One drug combination with three different dosages	15
Temple, Hamm (1996)	DCS	Two drug dosages	2
Hoffman, Cheng, Zafonte, Kline (2008)	Haloperidol Risperidone	Two drugs	2
Trabold, Krieg, Scholler, Plesnila (2008)	V-1880 (sigma) (AVP V1a) V-2381 (sigma) (AVP V2)	Two drugs targeting different receptors	2

Cont'd

Table 3.A Cont'd

Author	**Drug(s)**	**Rationale**	**Total $N_{Studies}$**
Mybe, Singh, Carrico, Saatman, Hall (2009)	Cyclosporin A NIM811	Two drugs	2
Longhi, Perego, Ortolano, Zanier, Bianchi, Stocchetti, McIntosh, De Simoni (2009)	C1-INH	Two time-to-treatment intervals	2

Table 3.B: Demographic and bibliographic details of included studies.

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
SEROTONERGIC TREATMENTS											
1. Kline, Yu et al (2002)	Rat (Sprague -Dawley)	9	9	CCI	NS	**8-OH-DPAT** (8-hydroxy-2-[di-n-propylamino]tetralin)	.5 mg/kg	15 minutes	18 days	14	Morris Water Maze
2. Kline, Wagner et al (2007)	Rat (Sprague -Dawley)	10	10	CCI	Moderate	**8-OH-DPAT** (8-hydroxy-2-[di-n-propylamino]tetralin)	.5 mg/kg	15 minutes	18 days	20	Morris Water Maze
3. Cheng Aslam Hoffman et al (2007)	Rat	12	12	CCI	NS	**8-OH-DPAT** (8-hydroxy-2-[di-n-propylamino]tetralin)	.5 mg/kg	15 minutes	18 days	14	Morris Water Maze
4. Cheng, Hoffman, et al. (2008)	Rat (Sprague -Dawley)	12	12	CCI	Moderate	**8-OH-DPAT** (8-hydroxy-2-[di-n-propylamino]tetralin)	.5mg/kg	24 hours	16 days	15	Morris Water Maze
CATECHOLAMINERGIC TREATMENTS											
5. Kline, Yan, Bao et al (2000)	Rat (Sprague -Dawley)	8	8	CCI	NS	**Methylphenidate** (Ritilan)	5 mg/kg	24 hours	18 days 4 days	14	Morris Water Maze Beam Walk

Cont'd

Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
6. Wagner, Kline et al (2007)	Rat	16	16	CCI	NS	**Methylphenidate** (Ritilan)	5 mg/kg	24 hours	5 days 13 days 19, 20 days	10	Beam Balance Beam Walk Open Field Test Morris Water Maze (speed, latency)
7. Zhu, Hamm, Reeves et al (2003)	Rat (Sprague -Dawley)	10	5	Central FPI	Moderate	**L-deprenyl**	1 mg/kg	24 hours	15 days	18	Morris Water Maze
8. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	21	24	Weight Drop	Mild	**Apomorphine**	0.3 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
9. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	19	24	Weight Drop	Mild	**Apomorphine**	1.0 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
10. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	17	24	Weight Drop	Mild	**Apomorphine**	3.0 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
11. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	20	19	Weight Drop	Mild	**Haloperidol**	0.3 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
12. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	24	19	Weight Drop	Mild	**Haloperidol**	1.0 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
13. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	23	19	Weight Drop	Mild	**Haloperidol**	3.0mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
14. Hoffman, Cheng, et al. (2008)	Rat (Sprague -Dawley)	12	12	CCI	NS	**Haloperidol**	0.5mg/kg	24 hours	19 days 2 days	16	Morris Water Maze Beam Walk
15. Hoffman, Cheng, et al. (2008)	Rat (Sprague -Dawley)	12	12	CCI	NS	**Risperidone**	0.45mg/kg	24 hours	19 days	16	Morris Water Maze
16. Kline et al. (2008)	Rat (Sprague -Dawley)	10	10	CCI	NS	**Risperidone**	4.5mg/kg	24 hours	18 days	15	Morris Water Maze
17. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	20	20	Weight Drop	Mild	**SCH-23390**	0.03mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
18. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	21	20	Weight Drop	Mild	**SCH-23390**	0.10mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
19. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	22	20	Weight Drop	Mild	**SCH-23390**	0.30 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
20. Tang & Nabeshima (1997b)	Mouse (ddY)	20	16	Weight Drop	NS	**SCH-23390**	0.03 mg/kg	15 minutes	9, 11 days	12	Water Finding Task (ambulation)
21. Tang & Nabeshima (1997b)	Mouse (ddY)	20	16	Weight Drop	NS	**SCH-23390**	0.30 mg/kg	15 minutes	9, 11 days	12	Water Finding Task (ambulation)
22. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	19	20	Weight Drop	Mild	**Sulpiride**	3.0 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
23. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	17	20	Weight Drop	Mild	**Sulpiride**	10.0 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
24. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	21	20	Weight Drop	Mild	**Sulpiride**	30.0 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
25.Tang & Nabeshima (1997b)	Mouse (ddY)	17	19	Weight Drop	NS	**Sulpiride**	3.0mg/kg	15 minutes	9, 11 days	12	Water Finding Task (ambulation)
26.Tang & Nabeshima (1997b)	Mouse (ddY)	17	19	Weight Drop	NS	**Sulpiride**	30.0mg/kg	15 minutes	9, 11 days	12	Water Finding Task (ambulation)
27.Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	19	17	Weight Drop	Mild	**Sulpiride +** **SCH-23390**	3.0mg/kg 0.03mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
28. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	21	17	Weight Drop	Mild	**Sulpiride** + **SCH-23390**	3.0 mg/kg 0.10 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
29. Tang, Noda, Nabeshima (1997a)	Mouse (ddY)	18	17	Weight Drop	Mild	**Sulpiride** + **SCH-23390**	3.0 mg/kg 0.30 mg/kg	15 minutes	NS	16	Water Finding Task (ambulation)
30. Tang & Nabeshima (1997b)	Mouse (ddY)	20	16	Weight Drop	NS	**Sulpiride** + **SCH-23390**	3.0 mg/kg 0.03 mg/kg	15 minutes	9, 11 days	12	Water Finding Task ambulation)
31. Tang & Nabeshima (1997b)	Mouse (ddY)	18	16	Weight Drop	NS	**Sulpiride** + **SCH-23390**	3.0 mg/kg 0.30 mg/kg	15 minutes	9, 11 days	12	Water Finding Task (ambulation)

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
32. Huang, Chen, Shohami, Weinstock (1999)	Mouse (Sabra)	8	8	Weight Drop	Severe	**Rasagiline**	1.0 mg/kg	5 minutes	11 days	14	Morris Water Maze
33. Huang, Chen, Shohami, Weinstock (1999)	Mouse (Sabra)	8	8	Weight Drop	Severe	**Rasagiline** + **Scopolamine**	1.0 mg/kg 0.2 mg/kg	5 minutes	11 days	14	Morris Water Maze
CHOLINERGIC TREATMENTS											
34. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	10	31	Weight Drop	Moderate	**Scopolamine**	0.2 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
35. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	11	31	Weight Drop	Moderate	**Scopolamine**	1.0 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
36. Chen, Shohami, Constantini et al (1998)	Mouse (Sabra)	12	12	Weight Drop	Severe	**Scopolamine**	1 mg/kg	5 minutes	14 days	18	Neurological Severity Score

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
37. Lyeth, Ray, Hamm et al (1992)	Rat (Sprague -Dawley)	9	9	Central FPI	Moderate	**Scopolamine**	1 mg/kg	15 minutes	5 days	14	Beam Walk, Beam Balance
38. Lyeth, Ray, Hamm et al (1992)	Rat (Sprague -Dawley)	10	10	Central FPI	Moderate	**Scopolamine**	1 mg/kg	30 minutes	5 days	14	Beam Walk, Beam Balance
39. Lyeth, Ray, Hamm et al (1992)	Rat (Sprague -Dawley)	11	10	Central FPI	Moderate	**Scopolamine**	1 mg/kg	60 minutes	5 days	14	Beam Walk, Beam Balance
40. Pike, Hamm (1997)	Rat (Sprague -Dawley)	9	8	Central FPI	Moderate	**LU 25-109-T**	15 umol/kg	24 hours	15 days	16	Morris Water Maze
41. Pike, Hamm (1997)	Rat (Sprague -Dawley)	6	8	Central FPI	Moderate	**LU 25-109-T**	3.6 umol/kg	24 hours	15 days	16	Morris Water Maze
42. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	7	31	Weight Drop	Moderate	**Mecamylamine**	2.5 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
43. Chen, Shohami, Constantini et al (1998)	Mouse (Sabra)	18	12	Weight Drop	Severe	**Mecamylamine**	2.5 mg/kg	5 minutes	14 days	18	Neurological Severity Score

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
44. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	14	31	Weight Drop	Moderate	**ENA713** (Rivastigmine)	0.2 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
45. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	8	31	Weight Drop	Moderate	**ENA713** (Rivastigmine)	1.0 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
46. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	32	31	Weight Drop	Moderate	**ENA713** (Rivastigmine)	2.0 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
47. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	14	31	Weight Drop	Moderate	**ENA713** (Rivastigmine)	2.0 mg/kg	60 minutes	24 hours	14	Neurological Severity Score
48. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	10	31	Weight Drop	Moderate	**ENA713** (Rivastigmine)	2.0 mg/kg	120 minutes	24 hours	14	Neurological Severity Score

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
49. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	21	31	Weight Drop	Moderate	**ENA713** (Rivastigmine)	5.0 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
50. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	5	31	Weight Drop	Moderate	**ENA713** (Rivastigmine)	5.0 mg/kg	60 minutes	24 hours	14	Neurological Severity Score
51. Chen, Shohami, Constantini et al (1998)	Mouse (Sabra)	11	12	Weight Drop	Severe	**ENA 713** (Rivastigmine)	1 mg/kg	5 minutes	14 days	18	Neurological Severity Score
52. Chen, Shohami, Constantini et al (1998)	Mouse (Sabra)	25	12	Weight Drop	Severe	**ENA 713** (Rivastigmine)	2 mg/kg	5 minutes	14 days	18	Neurological Severity Score
53. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	9	31	Weight Drop	Moderate	**ENA713** + **Scopolamine**	2.0 mg/kg 0.2 mg/kg	5 minutes	24 hours	14	Neurological Severity Score

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
54. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	11	31	Weight Drop	Moderate	**ENA713** + **Scopolamine**	2.0 mg/kg 1.0 mg/kg	5 minutes	24 hours	14	Neurological Severity Score
55. Chen, Shohami, Constantini et al (1998)	Mouse (Sabra)	19	12	Weight Drop	Severe	**ENA 713** (Rivastigmine) + **Scopolamine**	2.0 mg/kg 0.2 mg/kg	5 minutes	14 days	18	Neurological Severity Score
56. Chen, Shohami, Constantini et al (1998)	Mouse (Sabra)	12	12	Weight Drop	Severe	**ENA 713** (Rivastigmine) + **Scopolamine**	2.0 mg/kg 1.0 mg/kg	5 minutes	14 days	18	Neurological Severity Score
57. Chen, Shohami, Constantini et al (1998)	Mouse (Sabra)	15	12	Weight Drop	Severe	**ENA 713** (Rivastigmine) + **Mecamylamine**	2.0 mg/kg 2.5 mg/kg	5 minutes	14 days	18	Neurological Severity Score
58. Chen, Shohami, Bass, Weinstock (1998)	Rat (Sabra)	6	31	Weight Drop	Moderate	**ENA713** + **Mecamylamine**	2.0 mg/kg 2.5 mg/kg	5 minutes	24 hours	14	Neurological Severity Score

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
59. Pike, Hamm, Temple et al (1997)	Rat (Sprague -Dawley)	8	8	Central FPI	Moderate	**THA** (Tetrahydroaminoacridine)	1 mg/kg	24 hours	15 days	16	Morris Water Maze
60. Pike, Hamm, Temple et al (1997)	Rat (Sprague -Dawley)	10	8	Central FPI	Moderate	**THA** (Tetrahydroaminoacridine)	3 mg/kg	24 hours	15 days	16	Morris Water Maze
61. Pike, Hamm, Temple et al (1997)	Rat (Sprague -Dawley)	7	8	Central FPI	Moderate	**THA** (Tetrahydroaminoacridine)	9 mg/kg	24 hours	15 days	16	Morris Water Maze
MODULATORS OF CALCIUM HOMEOSTASIS											
62. Lee, Galo et al (2004)	Rat (Sprague -Dawley)	7	9	Lateral FPI	NS	**SNX-185**	50 pmol	5 minutes	42 days 18 days	16	Beam Walk Morris Water Maze
63. Lee, Galo et al (2004)	Rat (Sprague -Dawley)	6	9	Lateral FPI	NS	**SNX-185**	100 pmol	5 minutes	42 days 18 days	16	Beam Walk Morris Water Maze
64. Lee, Galo et al (2004)	Rat (Sprague -Dawley)	8	9	Lateral FPI	NS	**SNX-185**	200 pmol	5 minutes	42 days 18 days	16	Beam Walk Morris Water Maze

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
65. Berman, Verweij, Muizelaar (2000)	Rat (Sprague -Dawley)	9	8	Weight Drop	Moderate	**Ziconotide**	2 mg/kg	3 hours	24 hours 42 days 14 days	18	Inclined Plane Test Beam Balance, Beam Walk Radial Arm Maze
66. Cheney, Weisser et al (2001)	Rat (Sprague -Dawley)	10	13	Lateral FPI	NS	**BMS-204352**	0.03 mg/kg	10 minutes	42 hours	18	Morris Water Maze
67. Cheney, Weisser et al (2001)	Rat (Sprague -Dawley)	13	13	Lateral FPI	NS	**BMS-204352**	0.10 mg/kg	10 min	42 hours	18	Morris Water Maze
68. Kleindeinst, Harvey et al (2004)	Rat (Sprague -Dawley)	10	10	Lateral FPI	NS	**S100B**	.5 ul	NS	34 days	14	Morris Water Maze
THYROTROPIN-RELEASING HORMONE ANALOGUES											
69. Faden (1993)	Rat (Sprague -Dawley)	11	11	Lateral FPI	NS	**YM14673**	1.0 mg/kg	30 minutes	14 days	14	Composite Neuroscore
70. Faden (1993)	Rat (Sprague -Dawley)	11	11	Lateral FPI	NS	**YM14673** + **Nalmefene**	1.0 mg/kg 0.1 mg/kg	30 minutes	14 days	14	Composite Neuroscore

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
71. Faden, Fox, Araldi et al (1999)	Rat (Sprague -Dawley)	17	14	Lateral FPI	Moderate	**2-ARA-53a** (Thyrotropin-releasing hormone)	1 mg/kg	30 minutes	14 days	14	Composite Neuroscore
72. Faden, Knoblach et al (2003)	Rat (Sprague -Dawley)	11	11	Lateral FPI	Moderate	**TRH 35b**	1.0 mg/kg	30 minutes	17 days	16	Morris Water Maze
VASODILATORS											
73. Barone, Ohlstein, Hunter et al (2000)	Rat (Sabra)	6	6	Weight Drop	NS	**SB234551**	15.0 mg/kg	15 minutes	24 hours	12	Neurological Severity Score
74. Barone, Ohlstein, Hunter et al (2000)	Rat (Sabra)	6	6	Weight Drop	NS	**SB234551**	60.0 mg/kg	15 minutes	24 hours	12	Neurological Severity Score
75. Barone, Ohlstein, Hunter et al (2000)	Rat (Sabra)	6	6	Weight Drop	NS	**SB209670**	7.5 mg/kg	15 minutes	24 hours	12	Neurological Severity Score
76. Barone, Ohlstein, Hunter et al (2000)	Rat (Sabra)	6	6	Weight Drop	NS	**SB209670**	15.0 mg/kg	15 minutes	24 hours	12	Neurological Severity Score

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
77. Barone, Ohlstein, Hunter et al (2000)	Rat (Sabra)	6	6	Weight Drop	NS	**SB209670**	30.0 mg/kg	15 minutes	24 hours	12	Neurological Severity Score
78. Barone, Ohlstein, Hunter et al (2000)	Rat (Sabra)	6	6	Weight Drop	NS	**SB209670**	60.0 mg/kg	15 minutes	24 hours	12	Neurological Severity Score
OPIOIDS											
79. Redell, Moore et al (2003)	Rat (Long-Evans)	9	9	CCI	NS	**nor-BNI**	1 mg/ml	immediate post-injury	15 days	14	Morris Water Maze
80. Faden (1993)	Rat (Sprague-Dawley)	11	11	Lateral FPI	NS	**Nalmefene** + **Dextrorphan**	0.1 mg/kg 10.0 mg/kg	30 minutes	14 days	14	Composite Neuroscore
81. Faden (1993)	Rat (Sprague-Dawley)	11	11	Lateral FPI	NS	**Nalmefene**	0.1 mg/kg	30 minutes	14 days	14	Composite Neuroscore
82. Zohar, Getslev et al (2006)	Mouse (ICR)	15	15	Weight Drop	Mild	**Morphine**	10 mg/kg	Immediate post-injury	90 days	12	Morris Water Maze

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
ANTI-INFLAMMATORIES											
83. Knoblach & Faden (1998)	Rat (Sprague-Dawley)	18	17	Lateral FPI	NS	**IL-10**	100 ul	5 minutes	2 weeks	14	Composite Neuroscore
84. Yatsiv, Morganti-Kossman n et al (2002)	Mouse (Sabra)	18	16	Weight Drop	NS	**IL-18BP**	50 ug	1 hour	7 days	14	Neurological Severity Score
85. Hoane, Pierce, Holland et al (2007)	Rat	7	7	CCI	NS	**COG1410**	0.4mg/kg	30 minutes	14 days 23 days	12	Forelimb Placing Test, Limb-Use Asymmetry Test, Beam Walk Test
86. Hoane, Pierce, Holland et al (2007)	Rat	7	7	CCI	NS	**COG1410**	0.8mg/kg	30 minutes	14 days 23 days	12	Forelimb Placing Test, Limb-Use Asymmetry Test, Beam Walk Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
87. Hoane, Kaufman et al (2009)	Rat (Sprague-Dawley)	7	7	CCI	NS	**COG1410**	.8mg/kg	30 minutes	14 days 18 days	10	Bilateral Tactile Removal Test, Morris Water Maze (reference memory) Morris Water Maze (working memory)
88. Pillay, Kellaway et al (2007)	Rat	5	5	Lateral FPI	Severe	**VCP** (vaccinia virus complement control protein)	1.7 ug/ul	Immediate post-injury	5 days 4 days	8	Lateral left pulsion, Tactile placing Right lateral pulsion
89. Longhi, Perego et al (2009)	Mouse (C57B1/6)	12	12	CCI	NS	**C1-INH** (C1 inhibitor)	15U	10minutes	4 weeks	12	Morris Water Maze, Composite Neuroscore
90. Longhi, Perego et al (2009)	Mouse (C57B1/6)	12	12	CCI	NS	**C1-INH** (C1 inhibitor)	15U	1 hour	4 weeks	12	Morris Water Maze, Composite Neuroscore
91. Hoane, Akstulewicz, Toppen (2003)	Rat (Sprague-Dawley)	9	9	CCI	NS	**B3** (Nicotinamide)	500 mg/kg	15 minutes	10 days 17 & 20 days 30 days	12	Tactile Removal Test Morris Water Maze (latency) Fine Motor Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
92. Hoane, Tan, Pierce et al (2006)	Rat	10	11	Lateral FPI	Moderate	**B3** (Nicotinamide)	50mg/kg	15 minutes	35 days	16	Beam Walk, Adhesive Removal Test, Forelimb Placing, Morris Water Maze
93. Hoane, Tan, Pierce et al (2006)	Rat	11	11	Lateral FPI	Moderate	**B3** (Nicotinamide)	500mg/kg	15 minutes	35 days	16	Beam Walk, Adhesive Removal Test, Forelimb Placing Test, Morris Water Maze
94. Lu, Qu, Goussev et al (2007)	Rat	10	10	CCI	NS	**Atorvastatin**	1mg/kg	24 hours	15 days	16	Morris Water Maze
95. Lu, Qu, Goussev et al (2007)	Rat	10	10	CCI	NS	**Atorvastatin**	1mg/kg	24 hours	35 days	16	Morris Water Maze
96. Lu, Goussev, Chen et al (2004)	Rat (Wistar)	10	10	CCI	NS	**Atorvastatin**	1 mg/kg	24 hours	14 days	14	Mod. Neurological Severity Score, Corner Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
97. Lu, Mahmood, Goussev et al (2004)	Rat (Wistar)	4	4	CCI	NS	**Atorvastatin**	1 mg/kg	24 hours	15 days	14	Morris Water Maze
98. Lu, Qu, Goussev et al (2007)	Rat	10	10	CCI	NS	**Simvastatin**	1mg/kg	24 hours	35 days	16	Morris Water Maze
99. Lu, Qu, et al (2007)	Rat	10	10	CCI	NS	**Simvastatin**	1 mg/kg	24 hours	35 days	12	Morris Water Maze
100. Sanchez Mejia, Oma, Li, Friedlander (2001)	Mouse (C57BL)	8	8	Weight Drop	NS	**Minocycline**	90 mg/kg	30 minutes	4 days	12	Rotarod
101. Bye et al (2007)	Mouse	3 (est.)	3 (est.)	Weight drop	NS	**Minocycline**	45 mg/kg	30 minutes	4 days	14	Neurological Severity Score
102. Tabold, Krieg et al (2008)	Mouse (C57/B16)	8	8	CCI	NS	**V-1880** (AVP V_{1a})	500ng	3 minutes	7 days	14	Beam Walk

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose			Quality Score/20	Measure
ANTIDIURETICS											
103. Trabold, Krieg et al (2008)	Mouse (C57/B16)	8	8	CCI	NS	**V-2381** (AVP V_2)	500ng	3 minutes	7 days	14	Beam Walk
IMMUNOSUPPRESSANTS											
104. Mbye, Singh et al (2009	Mouse (CF-1)	12	12	CCI	Severe	**Cyclosporin A**	20mg/kg	15 minutes	7 days	13	Composite Neuroscore
105. Erlich, Alexandrovic h et al (2007)	Mouse (Sabra)	8	5	Weight Drop	NS	**Rapamycin**	0.5 mg/kg	4 hours	34 days	14	Neurological Severity Score
106. Erlich, Alexandrovic h et al (2007)	Mouse (Sabra)	7	5	Weight Drop	NS	**Rapamycin**	1.0 mg/kg	4 hours	34 days	14	Neurological Severity Score
MODULATORS OF FREE RADICAL FORMATION											
107. Louin, Marchand-Verrecchia et al (2006)	Rat (Sprague-Dawley)	17	19	Lateral FPI	NS	**AG**	20 mg/kg	6 hours	24 hours	14	Global Neurological Score

Cont'd

Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
108. Louin, Marchand-Verrecchia et al (2006)	Rat (Sprague-Dawley)	20	20	Lateral FPI	NS	**L-NIL**	100 mg/kg	6 hours	24 hours	14	Global Neurological Score
109. Louin, Marchand-Verrecchia et al (2006)	Rat (Sprague-Dawley)	13	12	Lateral FPI	NS	**1400W**	20 mg/kg	5 minutes	24 hours	14	Global Neurological Score
110. Louin, Marchand-Verrecchia et al (2006)	Rat (Sprague-Dawley)	15	15	Lateral FPI	NS	**1400W**	20 mg/kg	6 hours	24 hours	14	Global Neurological Score
111. Mesenge, Verrecchia et al (1996)	Mouse (Swiss)	14	16	Weight Drop	Moderate	**L-Name** (N^G–nitro-L-arginine methyl ester)	3 mg/kg	5 minutes	24 hours	16	Grip Test
112. Mesenge, Verrecchia et al (1996)	Mouse (Swiss)	15	16	Weight Drop	Moderate	**L-Name** (N^G–nitro-L-arginine methyl ester)	3 mg/kg	120 minutes	24 hours	16	Grip Test
113. Mesenge, Verrecchia et al (1996)	Mouse (Swiss)	19	20	Weight Drop	Moderate	**7-NI** (7-nitroindazole)	25 mg/kg	5 minutes	24 hours	16	Grip Test
114. Dixon, Ma, Marion (1997)	Rat (Sprague-Dawley)	10	10	CCI	NS	**CDP-choline** (cytidine-5-diphosphate)	100 mg/kg	24 hours	24 hours 18 days	12	Beam Balance, Beam Walk, Morris Water Maze

Cont'd

Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
115. Dempsey & Rao (2003)	Rat (Sprague -Dawley)	8	8	CCI	Moderate	**CDP-Choline**	100 mg/kg	immediate post-injury	7 days	14	Composite Neuroscore
116. Dempsey & Rao (2003)	Rat (Sprague -Dawley)	8	8	CCI	Moderate	**CDP-Choline**	200 mg/kg	immediate post-injury	7 days	14	Composite Neuroscore
117. Dempsey & Rao (2003)	Rat (Sprague -Dawley)	8	8	CCI	Moderate	**CDP-Choline**	400 mg/kg	immediate post-injury	7 days	14	Composite Neuroscore
118. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	19	20	Weight Drop	NS	**PBN**	50.0 mg/kg	5 minutes	24 hours	16	Grip Test
119. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	20	20	Weight Drop	NS	**PBN**	100.0 mg/kg	5 minutes	24 hours	16	Grip Test
120. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	23	22	Weight Drop	NS	**PBN**	100.0 mg/kg	5 minutes	24 hours	16	Grip Test
121. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	22	22	Weight Drop	NS	**PBN**	100.0 mg/kg	5 minutes	24 hours	16	Grip Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
122. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	23	22	Weight Drop	NS	**PBN**	100.0 mg/kg	5 minutes	24 hours	16	Grip Test
123. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	23	22	Weight Drop	NS	**PBN**	100.0 mg/kg	5 minutes	24 hours	16	Grip Test
124. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	19	20	Weight Drop	NS	**PBN**	200 mg/kg	5 minutes	24 hours	16	Grip Test
125. Marklund, Clausen et al (2001)	Rat (Sprague -Dawley)	9	8	Lateral FPI	Moderate	**PBN**	30 mg/kg	30 minutes	8 days	18	Combined Neurological Score, Inclined Plane Test
126. Marklund, Clausen et al (2001)	Rat (Sprague -Dawley)	7	8	Lateral FPI	Moderate	**S-PBN**	30 mg/kg	30 minutes	8 days	18	Combined Neurological Score, Inclined Plane Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
127. Lu, Mahmood, Zhang, Chopp (2003)	Rat (Wistar)	16	16	CCI	Severe	**DETA/NONOate** (Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl)amino] diazen-1-ium-1,2-diolate	0.4 mg/kg	24 hours	42 days	16	Modified Neurological Severity Score, Corner Test
128. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	15	15	Weight Drop	NS	**Melatonin**	1.25 mg/kg	5 minutes	24 hours	16	Grip Test
129. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	15	13	Weight Drop	NS	**Melatonin**	1.25 mg/kg	5 minutes	24 hours	16	Grip Test
130. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	15	13	Weight Drop	NS	**Melatonin**	1.25 mg/kg	30 minutes	24 hours	16	Grip Test
131. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	15	13	Weight Drop	NS	**Melatonin**	1.25 mg/kg	60 minutes	24 hours	16	Grip Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
132. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	15	15	Weight Drop	NS	**Melatonin**	0.63 mg/kg	5 minutes	24 hours	16	Grip Test
133. Mesenge, Margaill, Verrecchia et al (1998)	Mouse (Swiss)	15	15	Weight Drop	NS	**Melatonin**	2.50 mg/kg	5 minutes	24 hours	16	Grip Test
134. Hall, Kupina, Althaus (1999)	Mouse (CF-1)	31	36	Weight Drop	Severe	**PenME** (d-penicillamine methyl ester)	0.01 mg/kg	5 minutes	1 hour	14	Grip Test
135. Hall, Kupina, Althaus (1999)	Mouse (CF-1)	30	36	Weight Drop	Severe	**PenME** (d-penicillamine methyl ester)	0.1 mg/kg	5 minutes	1 hour	14	Grip Test
136. Hall, Kupina, Althaus (1999)	Mouse (CF-1)	35	36	Weight Drop	Severe	**PenME** (d-penicillamine methyl ester)	1.0 mg/kg	5 minutes	1 hour	14	Grip Test
137. Hall, Kupina, Althaus (1999)	Mouse (CF-1)	21	36	Weight Drop	Severe	**PenME** (d-penicillamine methyl ester)	10.0 mg/kg	5 minutes	1 hour	14	Grip Test
138. de la Torre (1995)	Mouse (CD-1)	8	8	Weight Drop	Moderate	**DMSO** (dimethyl sulfoxide)	1 gm/kg	5 minutes	2 hours	16	Grip Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
139. Barbre & Hoane (2006)	Rat (Sprague -Dawley)	6	6	CCI	NS	**B2** (Riboflavin)	7.5 mg/kg	1 hour	2 days 17 days	12	Bilateral Tactile Test Fine motor Test
140. Hoane, Wolyniak, Akstulewicz (2005)	Rat (Sprague -Dawley)	7	8	CCI	NS	**B2** (Riboflavin)	7.5 mg/kg	15 minutes	10 days 16 & 20 days	14	Tactile removal Test Morris Water Maze (reference memory, working memory latency)
141. Smith et al (2007)	Rat (Lister Hooded)	9	7	CCI	NS	**Inosine**	.5 ul/hr	Immediate post-injury	28 days 21 days	12	Staircase test, Cylinder test Ladder Walking
142. Knoblach & Faden (2002)	Rat (Sprague -Dawley)	14	10	Lateral FPI	Moderate	**Anti-ICAM-1**	1 mg/kg	1 hour	14 days	16	Composite Neuroscore
143. Knoblach & Faden (2002)	Rat (Sprague -Dawley)	10	10	Lateral FPI	Moderate	**Murine IgG**	1 mg/kg	1 hour	14 days	16	Composite Neuroscore
144. Zarubina (2003)	Rat (Albino)	10	10	CCI	Moderate	**Bemythyl** (2-ethyl-thiobenzimadasole hydrobromide)	25 mg/kg	NS	3 days	10	Open Field Test, Elevated Plus Maze, Spontaneous Motor Activity, Exploratory Activity, Emotional Activity

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
STEROIDS											
145. Goss, Hoffman, Stein (2003)	Rat (Sprague -Dawley)	8	9	CCI	NS	**Progesterone**	8 mg/kg	24 hours	16 & 18 days 8 days	14	Morris Water Maze (platform reaches, time spent in platform) Elevated Plus Maze
146. Goss, Hoffman, Stein (2003)	Rat (Sprague -Dawley)	7	9	CCI	NS	**Progesterone**	16 mg/kg	24 hours	16 & 18 days 8 days	14	Morris Water Maze (platform reaches, time spent in platform) Elevated Plus Maze
147. Goss, Hoffman, Stein (2003)	Rat (Sprague -Dawley)	7	9	CCI	NS	**Progesterone**	32 mg/kg	24 hours	16 & 18 days 8 days	14	Morris Water Maze (platform reaches, time spent in platform) Elevated Plus Maze
148. Kokiko, Murashov, Hoane (2006)	Rat (Sprague -Dawley)	8	8	CCI	NS	**Raloxifene**	3 mg/kg	15 minutes	18 days	14	Morris Water Maze, Adhesive Removal Test, Locomotor Placing Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
MODULATORS OF AMINO ACID ACTIVITY											
149. Leoni, Chen et al (2000)	Rat (Sprague -Dawley)	17	14	Lateral FPI	Moderate	**NPS 1506**	1 mg/kg	10 minutes	7 days	14	Morris Water Maze
150. Browne, Leoni et al (2004)	Rat (Sprague -Dawley)	12	9	Lateral FPI	NS	**NPS 1506**	1.15 mg.kg	15 minutes	8 months	14	Morris Water Maze
151. Shapira, Artru, Lam (1992)	Rat (Sprague -Dawley)	11	11	Weight Drop	NS	**Ketamine**	180 mg/kg	1 hour	48 hours	14	Neurological Severity Score
152. Shohami, Novikov, Bass (1995)	Rat (Sabra)	8	8	Weight Drop	NS	**HU-211**	5 mg/kg	4 hours	24 hours	16	Neurological Severity Score
153. Shohami, Novikov, Bass (1995)	Rat (Sabra)	8	8	Weight Drop	NS	**HU-211**	5 mg/kg	6 hours	24 hours	16	Neurological Severity Score
154. Shohami, Novikov, Bass (1995)	Rat (Sabra)	12	10	Weight Drop	NS	**HU-211**	5 mg/kg	1 hour	14 days	16	Morris Water Maze

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
155. Temple & Hamm (1996)	Rat (Sprague -Dawley)	9	8	Lateral FPI	Moderate	**DCS** (D-cycloserine)	10 mg/kg	24 hours	15 days	16	Morris Water Maze
156. Temple & Hamm (1996)	Rat (Sprague -Dawley)	8	8	Lateral FPI	Moderate	**DCS** (D-cycloserine)	30 mg/kg	24 hours	15 days	16	Morris Water Maze
157. Yaka et al (2007)	Mouse	9	9	Weight drop	NS	**DCS** (D-cycloserine)	10 mg/kg	24 hours	3 days	16	Object Recognition test
158. O'Dell, Hamm (1995)	Rat (Sprague -Dawley)	10	10	Central FPI	Moderate	**MDL 26,479** (Suritozole)	5 mg/kg	11 days	11 days	16	Morris Water Maze
159. O'Dell, Hamm (1995)	Rat (Sprague -Dawley)	10	10	Central FPI	Moderate	**MDL 26,479** (Suritozole)	10 mg/kg	11 days	11 days	16	Morris Water Maze
160. Okiyama, Smith, White, McIntosh (1998)	Rat (Sprague -Dawley)	11	11	Lateral FPI	Moderate	**CP-98,113**	5 mg/kg	15 minutes	2 weeks	16	Composite Neuroscore

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
161. Okiyama, Smith et al (1997)	Rat (Sprague -Dawley)	11	12	Lateral FPI	Moderate	**CP-98,113**	5 mg/kg	15 minutes	2 days	16	Morris Water Maze
162. Okiyama, Smith et al (1997)	Rat (Sprague -Dawley)	13	12	Lateral FPI	Moderate	**CP-101,581**	5 mg/kg	15 minutes	2 days	16	Morris Water Maze
163. Okiyama, Smith et al (1997)	Rat (Sprague -Dawley)	12	12	Lateral FPI	Moderate	**CP-101,606**	6.5 mg/kg	15 minutes	2 days	16	Morris Water Maze
164. Browne, Leoni et al (2004)	Rat (Sprague -Dawley)	12	9	Lateral FPI	NS	**MgSO** (Magnesium Sulphate)	125 umol	15 minutes	8 months	14	Morris Water Maze
165. Heath & Vink (1999)	Rat (Sprague -Dawley)	6	6	Weight Drop	Severe	**MgSO** (Magnesium Sulphate)	750 umol	30 minutes	24 hours	16	Rotarod
166. Heath & Vink (1998)	Rat (Sprague -Dawley)	8	8	Weight Drop	NS	**MgSO** (Magnesium Sulfate)	100 umoles/kg	30 minutes	24 hours	14	Rotarod
167. Fromm, Heath et al (2004)	Rat (Sprague -Dawley)	16	16	Weight Drop	NS	**MgSO** (Magnesium Sulphate)	250 umol/kg	30 minutes	7 days	12	Open Field Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
168. Bareyre, Saatman, Helfaer et al (1999)	Rat (Sprague -Dawley)	14	14	Lateral FPI	Moderate	**MgCl** (Magnesium Chloride)	125 umol	60 minutes	14 days	16	Composite Neuroscore
169. Barbre & Hoane (2006)	Rat (Sprague -Dawley)	6	6	CCI	NS	**MgCl** (Magnesium Chloride)	1 mmol/kg	1 hour	2 days 17 days	12	Bilateral Tactile Test Fine motor Test
170. Barbre & Hoane (2006)	Rat (Sprague -Dawley)	6	6	CCI	NS	**MgCl** (Magnesium Chloride) + **B2** (Riboflavin)	1 mmol/kg + 7.5 mg/kg	1 hour	2 days 17 days	12	Bilateral Tactile Test Fine motor Test
171. Hoane (2005)	Rat (Sprague -Dawley)	10	10	CCI	NS	**MgCl** (Magnesium Chloride)	1 mmol/kg	15 minutes	10 days	12	Tactile Removal Test, Morris Water Maze
172. Barbre & Hoane (2006)	Rat (Sprague -Dawley)	6	6	CCI	NS	½ **MgCl** (Magnesium Chloride) + ½ **B2** (Riboflavin)	.5 mmol/kg + 3.75 mg/kg	1 hour	2 days 17 days	12	Bilateral Tactile Test Fine motor Test
173. Baranova, Whiting, Hamm (2006)	Rat	9	9	Central FPI	Moderate	**Aniracetam**	25mg/kg	24 hours	15 days	14	Morris Water Maze

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
174. Baranova, Whiting, Hamm (2006)	Rat	9	9	Central FPI	Moderate	**Aniracetam**	50mg/kg	24 hours	15 days	14	Morris Water Maze
175. Faden (1993)	Rat (Sprague -Dawley)	11	11	Lateral FPI	NS	**Dextrophan**	10.0 mg/kg	30 minutes	2 weeks	14	Composite Neuroscore
176. Hogg, Peron et al (1998)	Rat (Sprague -Dawley)	9 (est.)	9 (est.)	Lateral FPI	NS	**Eliprodil**	1 mg/kg	15 minutes	6 days	14	Freezing Response
GROWTH FACTORS											
177. Marklund, Bareyre, Royo et al (2007)	Rat (Sprague -Dawley)	13	11	Lateral FPI	Moderate	**mAb 7B12**	5 ul/hour	24 hours	30 days	16	Composite Neuroscore, Morris Water Maze
178. Sinson, Perri, Trojanowski et al (1997)	Rat (Sprague -Dawley)	12	12	Lateral FPI	Moderate	**NGF** (Nerve Growth Factor)	0.5 ul/hr	24 hours	4 weeks	16	Morris Water Maze
179. Dixon, Flinn et al (1997)	Rat (Sprague -Dawley)	10	10	CCI	NS	**NGF** (Nerve Growth Factor)	25 ug/ml	Immediate post-injury	7 days	14	Morris Water Maze

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
180. Lu, Mahmood, Qu, et al (2005)	Rat (Wistar)	6	6	CCI	NS	**EPO + BrdU** (erythropoieten)	5000 IU/kg	24 hours	15 days	14	Morris Water Maze
181. Yatsiv, Grigoriadis, et al (2005)	Mouse (Sabra)	18	18	Weight Drop	NS	**EPO** (Erythropoietin)	5000 U rhEpo/kg	1 hour	3 days	14	Neurological Severity Score, Object Recognition Test
OTHER											
182. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	17	18	Weight Drop	Mild	**VA-045**	0.5 mg/kg	30 min	48 & 96 hours	16	Water Finding Task (retention, retest)
183. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	18	18	Weight Drop	Mild	**VA-045**	1.0 mg/kg	30 min	48 & 96 hours	16	Water Finding Task (retention, retest)

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
184. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	15	18	Weight Drop	Mild	**VA-045**	2.0 mg/kg	30 minutes	48 & 96 hours	16	Water Finding Task (retention, retest)
185. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	18	18	Weight Drop	Mild	**VA-045**	4.0 mg/kg	30 minutes	48 & 96 hours	16	Water Finding Task (retention, retest)
186. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	18	17	Weight Drop	Mild	**VA-045**	0.5 mg/kg	30 minutes	48 & 96 hours	16	Water Finding Task (retention, retest)
187. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	19	17	Weight Drop	Mild	**VA-045**	1.0 mg/kg	30 minutes	48 & 96 hours	16	Water Finding Task (retention, retest)

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
188. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	20	17	Weight Drop	Mild	**VA-045**	2.0 mg/kg	30 minutes	48 & 96 hours	16	Water Finding Task (retention, retest)
189. Tang, Noda, Hosegawa, Nabeshima (1997)	Mouse (ddY)	19	17	Weight Drop	Mild	**VA-045**	4.0 mg/kg	30 minutes	48 & 96 hours	16	Water Finding Task (retention, retest)
190. Tang, Noda, Hasegawa, Nabeshima (1997)	Mouse (ddY)	19	16	Weight Drop	Mild	**VA-045**	0.5 mg/kg	30 minutes	11 days	14	Water Finding Task
191. Tang, Noda, Hasegawa, Nabeshima (1997)	Mouse (ddY)	17	16	Weight Drop	Mild	**VA-045**	1.0 mg/kg	30 minutes	11 days	14	Water Finding Task

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
192. Tang, Noda, Hasegawa, Nabeshima (1997)	Mouse (ddY)	16	16	Weight Drop	Mild	**VA-045**	2 mg/kg	30 minutes	11 days	14	Water Finding Task
193. Tang, Noda, Hasegawa, Nabeshima (1997)	Mouse (ddY)	19	16	Weight Drop	Mild	**VA-045**	4 mg/kg	30 minutes	11 days	14	Water Finding Task
194. Panikashvili et al (2001)	Mouse	10	10	Weight drop	NS	**2-AG** (2-Arachidonoyl glycerol)	0.1 mg/kg	15 minutes	24 hours	10	Neurological Severity Score
195. Panikashvili et al (2001)	Mouse	10	10	Weight drop	NS	**2-AG** (2-Arachidonoyl glycerol)	5.0 mg/kg	15 minutes	24 hours	10	Neurological Severity Score
196. Panikashvili et al (2001)	Mouse	10	10	Weight drop	NS	**2-AG** (2-Arachidonoyl glycerol)	10.0 mg/kg	15 minutes	24 hours	10	Neurological Severity Score

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
197. Clark, Vagni et al (2007)	Mouse (C57BL/6J)	11	11	CCI	Moderate	**INO-1001**	1.6 mg/kg	immediate post-injury	20 days	16	Morris Water Maze
198. Holloway et al (2007)	Rat	10	10	Lateral FPI	NS	**Lactate**	10 mM	30 minutes	15 days	14	Morris Water Maze
199. Holloway et al (2007)	Rat	10	10	Lateral FPI	NS	**Lactate**	28 mM	30 minutes	15 days	14	Morris Water Maze
200. Holloway et al (2007)	Rat	10	10	Lateral FPI	NS	**Lactate**	100 mM	30 minutes	15 days	14	Morris Water Maze
201. Holloway et al (2007)	Rat	10	10	Lateral FPI	NS	**Lactate**	280 mM	30 minutes	15 days	14	Morris Water Maze
202. Rice, Zsoldos et al (2002)	Rat (Sprague-Dawley)	9	9	Lateral FPI	Moderate	**Lactate**	100mM	30 minutes	15 days	14	Morris Water Maze
203. de la Torre (1995)	Mouse (CD-1)	8	8	Weight Drop	Moderate	**FDP** (fructose)	350 mg/kg	5 minutes	2 hours	16	Grip Test
204. de la Torre (1995)	Mouse (CD-1)	8	8	Weight Drop	Moderate	**FDP** (fructose) + **DMSO** (dimethyl sulfoxide)	350 mg/kg 1 gm/kg	5 minutes	2 hours	16	Grip Test

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
205. Belayev, Alonso, Huh et al (1999)	Rat (Sprague-Dawley)	8	9	Lateral FPI	NS	**HSA** (Human Serum Albumin)	1% body weight	15 minutes	7 days	14	Composite Neuroscore
206. Thornton, Vink et al (2006)	Rat (Sprague-Dawley)	1	5	Weight Drop	Severe	**sAPPa** (soluble amyloid precursor protein, a form)	5 uL/min	30 minutes	7 days	14	Rota rod
207. Mbye, Singh et al (2009	Mouse (CF-1)	12	12	CCI	Severe	**NIM811**	20mg/kg	15 minutes	7 days	13	Composite Neuroscore
208. Marciano, Shohami et al (2007)	Rat (Sabra)	7	7	Weight Drop	Moderate	**FTS** (S-trans-trans-farnesylthiosalicylic acid)	5 mg/kg	1 hour	7 days	20	Neurological Severity Score
209. Shohami, Yatsiv et al (2003)	Mouse (C57b1)	10	10	Weight Drop	NS	**FTS** (s-trans-trans-farnesylthioslicylic acid)	5 mg/kg	1 hour	7 days	14	Neurological Severity Score
210. Wang, Gao et al (2006)	Mouse (C57BL/6)	14	9	CCI	NS	**Levetiracetam**	18 mg/kg	30 minutes	5 days	12	Rotarod
211. Wang, Gao et al (2006)	Mouse (C57BL/6)	14	9	CCI	NS	**Levetiracetam**	54 mg/kg	30 minutes	5 days	12	Rotatod

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Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
212. Shapira, Yadid, Cotev, Shohami (1989)	Rat (Sabra)	9	8	Weight Drop	NS	**OKY-046** (E-3-[4-(1-Imidazolyl methyl) phenyl]-2-propenoic acid hydrochloride)	100 mg/kg	immediate post-injury	24 hours	12	Neurological Severity Score
213. Ji, Kim, Park et al (2005)	Rat (Sprague-Dawley)	6	6	CCI	NS	**GTSs** (Ginseng)	100 mg/kg	immediate post-injury	24 hours	16	Beam balance, Rotarod, Posture Reflex
214. Ji, Kim, Park et al (2005)	Rat (Sprague-Dawley)	6	6	CCI	NS	**GTSs** (Ginseng)	200 mg/kg	immediate post-injury	24 hours	16	Beam balance, Rotarod, Posture Reflex
215. Chong & Feng (2000)	Mouse (Kunming)	21	22	Weight Drop	NS	**NBP** (dl-3-n-butyphthalide)	12.5 mg/kg	5 minutes	24 hours	14	Memory Task
216. Chong & Feng (2000)	Mouse (Kunming)	20	22	Weight Drop	NS	**NBP** (dl-3-n-butyphthalide)	25.0 mg/kg	5 minutes	24 hours	14	Memory Task
217. Chong & Feng (2000)	Mouse (Kunming)	26	22	Weight Drop	NS	**NBP** (dl-3-n-butyphthalide)	50.0 mg/kg	5 & 60 minutes	24 hours	14	Memory Task
218. Hayashi, Shimada, Yasuda, Ikegami (1994)	Mouse (ddY)	17	42	Weight Drop	Severe	**Nizofenone**	0.3 mg/kg	60 minutes	6 days	14	Grip Test

Cont'd

Table 3.B Cont'd

Study Name	Animal	Treatment Group N	Control Group N	Injury Model	Injury Severity	Treatment Drug	Drug Dose	Time to Treatment	Time to Testing	Quality Score/20	Measure
219. Hayashi, Shimada, Yasuda, Ikegami (1994)	Mouse (ddY)	17	42	Weight Drop	Severe	**Nizofenone**	1.0 mg/kg	60 minutes	6 days	14	Grip Test
220. Hayashi, Shimada, Yasuda, Ikegami (1994)	Mouse (ddY)	28	42	Weight Drop	Severe	**Nizofenone**	3.0 mg/kg	60 minutes	6 days	14	Grip Test
221. Zarubina (2003)	Rat (Albino)	10	10	CCI	Moderate	**Pyracetum**	60 mg/kg	NS	3 days	10	Open Field Test, Elevated Plus Maze, Spontaneous Motor Activity, Exploratory Activity, Emotional Activity
222. Besson, Chen et al (2005)	Rat (Sprague -Dawley)	5	8	Lateral FPI	Moderate	**Fenofibrate**	50 mg/kg	6 hours	7 days	14	Global Neurological Score
223. Besson, Chen et al (2005)	Rat (Sprague -Dawley)	6	8	Lateral FPI	Moderate	**Fenofibrate**	100 mg/kg	6 hours	7 days	14	Global Neurological Score

Note: FPI = fluid percussion injury; CCI = controlled cortical impact; NS = not specified

Table 3.C: Chemical group and method of action of drugs

Chemical Group	**Method of Action**	**Drug**
Serotonergic	5-HT1A receptor agonist	8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetraline)
Catecholamines	Catecholamine transport inhibitor	Methylphenidate (Ritilan)
	Selective MAO-B inhibitor	L-deprenyl
	D2 receptor agonist	Apomorphine
	D2 receptor antagonist	Haloperidol
	D2 receptor antagonist (also a serotonin antagonist)	Risperidone
	D 1 receptor antagonist	SCH-23390
	D 2 receptor antagonist	Sulpiride
	Selective MAO-B inhibitor	Rasagiline
Cholinergic	Muscarinic receptor antagonist	Scopolamine
	Partial muscarinic M1 agonist and M2 antagonist	LU 25-109-T
	Nicotinic receptor antagonist	Mecamylamine
	Acetylcholinesterase inhibitor	ENA 713 (Rivastigmine)
	Acetylcholinesterase inhibitor	THA (Tetrahydroaminoacridine)
Modulators of calcium homeostasis	N-type **c**alcium channel blocker	SNX-185
	N-type calcium channel blocker	Ziconotide
	Maxi-K channel opener	BMS-204352
	Non-selective **c**alcium binding protein	S100B
Thyrotropin-Releasing Hormone analogues	TRH analogue	YM 14673
	TRH analogue	2-ARA-53a
	TRH analogue	TRH 35b (Diketopiperazine)
Vasodilators	Selective endothelin-A-receptor antagonist	SB 234551

cont'd

Table 3.C Cont'd

Chemical Group	Method of Action	Drug
	Selective endothelin-A-receptor antagonist	SB 209670
Opioids	Selective kappa-opioid antagonist	nor-BNI (Nor-binaltorphimine)
	Non-selective Opioid antagonist	Nalmefene
	Non-selective Opioid agonist, analgesic	Morphine
Anti-inflammatories	Cytokine synthesis inhibitor	IL-10 (Interleukin-10)
	Specific IL-18 inhibitor	IL-18BP
	Apolipoprotein E-mimetic	COG 1410
	Pro-inflammatory complement inhibitor	VCP (vaccinia virus complement control protein)
	C1 esterase inhibitor	C1-INH
	Vitamin/anti-inflammatory	B3 (Nicotinamide)
	HMG-CoA reductase inhibitor, anti-inflammatory	Atorvastatin
	HMG-CoA reductase inhibitor, anti-inflammatory	Simvastatin
	Tetracycline antibiotic, antioxidant, anti-inflammatory	Minocycline HCI
Antidiuretics	Antidiuretic, Selective AVP V_{1a}-receptor antagonist	V-1880 (Sigma)
	Antidiuretic, Selective AVP V_2-receptor antagonist	V-2381 (Sigma)
Immunosuppressants	Binds cyclophilin, inhibits mitochondrial permeability transition	Cyclosporin A
	Serine/threonine kinase inhibitor, immunosuppressant, antibiotic	Rapamycin
Modulators of free radical formation	NOS inhibitor	AG (aminoguanidine)
	NOS inhibitor	L-NIL (L-N-iminoethyl-lysine)
	NOS inhibitor	1400W

cont'd

Table 3.C Cont'd

Chemical Group	Method of Action	Drug
	NOS inhibitor	L-NAME (N^G-nitro-L-argine methyl ester)
	NOS inhibitor	7-NI (7-nitroindazole)
	Phospholipid intermediate and inhibitor of free radical production	CDP-choline
	Free radical scavenger	PBN (a-phenyl)-N-tert-butyl) nitrone
	Free radical scavenger	S-PBN (2-sulfo-phenyl-N-tert-butyl nitrone)
	Nitric oxide donor	DETA/NONOate (2)-1-[N-(2-aminoethyl)-N-(2-amminioethyl)amino]diazen-1-1um-1,2-diolate)
	Free radical scavenger	Melatonin
	Free radical scavenger	Pen ME (d-penicillamine methyl ester)
	Free radical scavenger	DMSO (Dimethyl sulfoxide)
	Oxygen radical scavenger	B2 (Riboflavin)
	Nucleoside	Inosine
		Anti-ICAM-1 (intracellular adhesion molecule-1)
		Murine IgG
	Antioxidant	Bemithyl
Steroids	Progesterone receptor modulator, antioxidant	Progesterone
	Selective oestrogen receptor modulator	Raloxifene
Modulators of Amino Acid activity	NMDA receptor antagonist	NPS 1506
	NMDA receptor antagonist	Ketamine
	NMDA receptor antagonist	HU-211 (Dexanabinol)
	Partial NMDA agonist	DCS (D-cycloserine)

cont'd

Table 3.C Cont'd

Chemical Group	Method of Action	Drug
	GABAA receptor modulator	MDL 26,479 (Suritozol)
	NMDA antagonist	CP-98,113
	NMDA antagonist	CP-101,581
	NMDA antagonist	CP-101,606
	NMDA antagonist, inhibits glutamate release	$MgSO_4$ (Magnesium Sulphate)
	NMDA antagonist, inhibits glutamate release	$MgCl_2$ (Magnesium Chloride)
	AMPA/Kainate agonist	Aniracetam
	Non-competitive NMDA antagonist	Dextrorphan
	NMDA antagonist	Eliprodil
Growth Factors	Anti-Nogo-A monoclonal antibody	mAB 7B12
	Nerve growth factor	NGF
	Cell-growth mediating substance	EPO (erythropoietin)
Other	Na^+ channel inhibitor, phosphodiesterase type 1 inhibitor	VA-045 (2-(nitrooxy)-ethyl apovincaminate)
	Cannabinoid, CB1 receptor agonist	2-AG (arachidonoyl glycerol)
	PARP-1 inhibitor	INO-1001
	Energy substrate	Lactate
	Glycolytic intermediate	FDP (Fructose)
	Antioxidant	HSA (human serum albumin)
	Neurotrophic, protects against metabolic and excitotoxic insults	sAPPalpha (soluble APP)
	Cyclophilin inhibitor, inhibits mitochondrial permeability transition	NIM811
	Ras protein inhibitor	FTS (S-trans-trans-farnesylthiosalicylic acid)

cont'd

Table 3.C Cont'd

Chemical Group	Method of Action	Drug
	Anticonvulsant (synaptic vesicle protein SV2A inhibitor)	Levetiracetam
	Thromboxane A2 synthetase inhibitor	OKY-046
	Vitanutrient	GTSs (Ginseng total saponin)
	Anti-apoptotic	NBP (dl-3-n-butylphthalide)
	Anionic channel blocker inhibiting glutamate release	Nizofenone
	Ion channel modulator (calcium, sodium, potassium)	Piracetum
	PPARa agonist	Fenofibrate
	Nucleoside	BrdU (Bromodeoxyuridine)

Note: TRH = thyrotopin-releasing hormone; MAO-B = monoamine oxidase B;

NMDA = N-methyl-d-aspartate antagonist; PPARa = peroxisome proliferators activated receptor a agonist;

mTOR = mammalian target of rapamycin; AMPA = a-amino-3-hydroxy-5-methyl-4-isoxazole propionate;

PARP = poly(ADP-ribose) polymerase-1; iNOS = inducible nitric oxide synthase.

Appendix 3.A: Quality Control Tool

		Score
1.	Is the control group matched to the treatment group on initial injury severity (i.e. matched on 1 hour NSS)	**1**
2.	Is the control group matched to the treatment group on motor performance in cognitive tasks (i.e. swim speed on MWM)	**1**
3.	Have animals been randomly allocated to groups	**1**
4.	Has the method of randomization been detailed	**1**
5.	Is the cognitive or motor test used described (or a reference provided)	**1**
6.	Are the test scores for each test/sub-test specified (i.e. speed, latency, % time)	**1**
7.	Is the age/weight of the animals specified (i.e. M, SD, range)	**1**
8.	Is the severity of injury specified (i.e. mild, moderate, severe)	**1**
9.	Is the gender of the animals specified	**1**
10.	Is the model of experimental trauma specified	**1**
11.	Is the model of experimental trauma described (or a reference provided)	**1**
12.	Is the initial sample size for each group specified	**1**
13.	Is the time from injury to treatment specified	**1**
14.	Is the time/s from treatment to testing specified	**1**
15.	Is the dosage of administered drug/s specified	**1**
16.	Are significant test statistics provided that would enable the calculation of an effect size: - Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value	**1**
17.	Is the N for each group on each testing occasion reported	**1**
18.	Are non-significant test statistics reported that would enable the calculation of an effect size: - Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value for significance	**1**
19.	Is group allocation (i.e. TBI Vs Control group) blinded to the	

	person conducting the cognitive/motor performance tests	**1**
20.	Is the number of animals lost to trauma specified	**1**
		TOTAL

Appendix 3.B : Quality rating grouped from highest to lowest quality

5	= Highest quality	Score 17 – 20	($N_{Studies}$ = 15; 7.0%)
4	= High quality	Score 13 – 16	($N_{Studies}$ = 161; 75.0%)
3	= Moderate quality	Score 9 – 12	($N_{Studies}$ = 37; 17.5%)
2	= Lower quality	Score 5 – 8	($N_{Studies}$ = 1; 0.5%)
1	= Lowest quality	Score 0 – 4	($N_{Studies}$ = 0)

Table 3.D: Serotonergic treatments

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
8-OH-DPAT													
Morris Water Maze	Cognitive	4	23	15-1440	moderate/not specified	CCI	.80	1.62	-.26 – 1.85	15	53	high/highest	Kline, Yu et al., 2002; Kline, Wagner et al., 2007; Cheng, Aslam et al., 2007; Cheng, Hoffman et al., 2008

Note: CCI = controlled cortical impact injury

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.E: Catecholaminergic treatments

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Rasagiline													
Morris Water Maze*	Cognitive	1	16	5	severe	WD	2.02		.70 – 3.34	9	19	high	Huang et al., 1999
Haloperidol													
Beam Walk	Motor	1	24	1,440	not specified	CCI	-1.49		-2.46 - -.52	7	29	high	Hoffman, Cheng et al., 2008
Water Finding Task*	Motor	3	42	15	mild	WD	-.24	.34	-.87 - .38	3	85	high	Tang, Noda et al., 1997c
Morris Water Maze	Cognitive	1	24	1,440	not specified	CCI	-.11		-.91 - .69	1	92	high	Hoffman, Cheng et al., 2008
Methylphenidate													
Beam Balance	Motor	1	32	1,440	not specified	CCI	1.48		.63 – 2.33	6	29	moderate	Wagner, Kline et al., 2007
Open Field Test	Behaviour	1	32	1,440	not specified	CCI	.60		-.46 – 1.65	2	62	moderate	Wagner, Kline et al., 2007
Morris Water Maze	Motor	1	32	1,440	not specified	CCI	.39		-.31 – 1.10	1	73	moderate	Wagner, Kline et al., 2007
Morris Water Maze	Cognitive	2	24	1,440	not specified	CCI	.32	1.08	-.75 – 1.17	2	79	moderate/high	Kline, Yan et al., 2000;Wagner, Kline et al., 2007

Cont'd

Table 3.E Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Beam Walk	Motor	2	24	1,440	not specified	CCI	.16	.58	-.55 – 1.17	1	85	moderate/high	Kline, Yan et al., 2000;Wagner, Kline et al., 2007
L-deprenyl													
Morris Water Maze	Cognitive	1	15	1,440	moderate	Central FPI	1.01		.04 – 1.98	4	45	highest	Zhu et al., 2000
Risperidone													
Morris Water Maze	Cognitive	2	44	1,440	NS	CCI	-.53	1.39	-1.84 - .11	8	48	high	Hoffman, Cheng et al., 2008; Kline et al., 2008
Sulpiride													
Water Finding Task*	Motor	5	75	15	not specified/mild	WD	-.37	.11	-1.02 - .28	8	73	moderate/high	Tang, Noda et al., 1997c,d
Rasagiline + Scopolamine													
Morris Water Maze*	Cognitive	1	16	5	severe	WD	-.31		-1.30 - .68	1	79	high	Huang, Chen et al., 1999

Cont'd

Table 3.E Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Sulpiride + SCH 23390													
Water Finding Task*	Motor	5	72	15	not specified/mild	WD	-.30	.27	-.99 - .35	7	79	moderate/high	Tang, Noda et al., 1997 c, d
Apomorphine													
Water Finding Task*	Motor	3	43	15	mild	WD	.26	.14	-.35 - .87	3	79	high	Tang, Noda et al., 1997c
SCH 23390													
Water Finding Task*	Motor	5	77	15	not specified/mild	WD	-.12	.43	- .84 - .48	2	92	moderate/high	Tang, Noda et al., 1997c, d

Note: WD = Weight drop injury; CCI = controlled cortical impact injury; Central FPI = central fluid percussion injury

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.F: Cholinergic treatments

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
LU 25-109-T													
Morris Water Maze	Cognitive	2	16	1,440	moderate	Central FPI	1.27	.88	.16 – 2.55	12	35	high	Pike & Hamm, 1997
ENA 713 + Scopolamine													
NSS	Motor	2	41	5	moderate	WD	-1.23	.77	-1.45 - .04	11	38	high	Chen, Shohami , Bass et al., 1998
NSS*	Motor	2	28	5	severe	WD	.25	.05	-.52 – 1.03	2	79	highest	Chen, Shohami, Constantini et al., 1998
ENA 713													
NSS*	Motor	2	30	5	severe	WD	1.07	2.40	.72 – 2.81	10	41	highest	Chen, Shohami, Constantini et al., 1998
NSS	Motor	7	46	120	moderate	WD	-.70	.88	-1.45 - .03	24	57	high	Chen, Shohami, Bass et al., 1998

Cont'd

Table 3.F Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Scopolamine													
NSS*	Motor	1	24	5	severe	WD	.82		-.04 – 1.68	3	53	highest	Chen, Shohami, Constantini et al., 1998
NSS	Motor	2	42	5	moderate	WD	.66	.77	-1.45 - .04	6	57	high	Chen, Shohami, Bass et al, 1998
Beam Balance	Motor	3	20	15-60	moderate	Central FPI	.49	.22	-.41 – 1.41	6	67	high	Lyeth et al., 1992
Beam Walk	Motor	3	20	15-60	moderate	Central FPI	.41	.59	-.44 – 1.41	5	73	high	Lyeth et al., 1992
ENA 713 + Mecamylamine													
NSS	Motor	1	37	5	moderate	WD	-.71		-1.61 - .19	3	57	high	Chen, Shohami, Bass et al., 1998
NSS*	Motor	1	27	5	severe	WD	.43		-.34 – 1.20	1	73	highest	Chen, Shohami, Constantini et al., 1998

Cont'd

Table 3.F Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
THA													
Morris Water Maze	Cognitive	3	16	1,440	moderate	Central FPI	.63	.60	-.34 – 1.75	9	62	high	Pike, Hamm et al., 1997
Mecamylamine													
NSS*	Motor	1	30	5	severe	WD	.17		-.56 - .90	0	85	highest	Chen, Shohami, Constantini et al., 1998
NSS	Motor	1	38	5	moderate	WD	-.06		-.88 - .76	1	92	high	Chen, Shohami, Bass et al., 1998

Note: Central FPI = central fluid percussion injury; WD = weight drop injury; NSS = Neurological Severity Score

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.G: Modulators of calcium homeostasis

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
SNX-185													
Morris Water Maze	Cognitive	3	15	5	not specified	Lateral FPI	2.17	1.21	1.06 – 4.15	32	16	high	Lee, Galo et al., 2004
Beam Walk	Motor	3	15	5	not specified	Lateral FPI	.85	.37	-.19 – 1.95	12	48	high	Lee, Galo et al., 2004
Ziconotide													
Beam Walk	Motor	1	17	180	moderate	WD	1.70		.50 – 2.90	8	25	highest	Berman et al., 2000
Inclined Plane Test	Motor	1	17	180	moderate	WD	1.42		.29 – 2.55	6	32	highest	Berman et al., 2000
Radial Arm Maze	Motor	1	17	180	moderate	WD	1.43		.30 – 2.56	6	32	highest	Berman et al., 2000
Beam Balance	Motor	1	17	180	moderate	WD	1.17		.09 – 2.24	5	38	highest	Berman et al., 2000
S100B													
Morris Water Maze	Cognitive	1	20	60	not specified	Lateral FPI	.63		-.28 – 1.54	2	62	high	Kleindeinst et al., 2004

Cont'd

Table 3.G Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
BMS-204352													
Morris Water Maze	Motor	2	25	10	not specified	Lateral FPI	-.11	.15	-.90 - .69	0	92	highest	Cheney et al., 2001

Note: Lateral FPI = lateral fluid percussion injury; WD = weight drop injury; CCI = controlled cortical impact injury

*Findings based on a mouse model of TBI. All other findings based on a rat model of TBI.

Table 3.H: Thyrotropin-Releasing hormone analogues

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
TRH 35b													
Morris Water Maze	Cognitive	1	22	30	moderate	Lateral FPI	5.70		3.14 – 8.25	28	2	high	Faden, Knoblach et al., 2003
YM 14673													
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.43		.43 – 2.43	6	32	high	Faden, 1993
YM 14673 + Nalmefene													
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.33		.35 – 2.31	6	35	high	Faden, 1993
2-ARA-53a													
Composite Neuroscore	Motor	1	31	30	moderate	Lateral FPI	.93		.16 – 1.70	4	48	high	Faden, Fox et al., 1999

Note: Lateral FPI = lateral fluid percussion injury

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.I: Vasodilators

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
SB 209670													
NSS	Motor	4	12	15	not specified	WD	1.94	1.85	1.03 – 4.81	38	21	moderate	Barone, Ohlstein et al., 2000
SB 234551													
NSS	Motor	2	12	15	not specified	WD	1.56	.97	.31 – 3.18	15	45	moderate	Barone, Ohlstein et al., 2000

Note: WD = weight drop injury; NSS = Neurological Severity Score

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.J: Opioids

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Nalmefene + Dextrorphan													
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.25		.29 – 2.21	5	35	high	Faden, 1993
Nalmefene													
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	.77		-.12 – 1.66	3	53	high	Faden, 1993
Nor-BNI													
Morris Water Maze	Motor	1	18	5	not specified	CCI	.58		-.37 – 1.54	2	62	high	Redell et al., 2003
Morphine													
Morris Water Maze*	Cognitive	1	30	5	mild	WD	-.34		-1.07 - .40	1	79	moderate	Zohar et al., 2006

Note: Lateral FPI = lateral fluid percussion injury; CCI = controlled cortical impact injury; WD = weight drop injury

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.K: Anti-inflammatories

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
B3 (Nicotinamide)													
Forelimb Placing Test	Motor	2	22	15	moderate	Lateral FPI	4.09	2.68	2.96 – 7.37	40	2	high	Hoane, Tan et al., 2006
Tactile Removal Test	Motor	1	18	15	not specified	CCI	3.10		1.51 – 4.69	15	7	moderate	Hoane, Akstulewicz et al., 2003
Morris Water Maze	Cognitive	3	20	15	moderate	CCI & Lateral FPI	.91	.37	-.02 – 1.90	13	48	moderate /high	Hoane, Akstulewicz et al., 2003; Hoane, Tan et al., 2006
Beam Walk	Motor	2	22	15	moderate	Lateral FPI	.60	.16	-.28 – 1.48	5	62	high	Hoane, Tan et al., 2006
Adhesive Removal Test	Motor	2	22	15	moderate	Lateral FPI	.21	.25	-.64 – 1.06	1	85	high	Hoane, Tan et al., 2006
Fine Motor Test	Motor	1	18	15	not specified	CCI	.06		-.86 - .99	1	92	moderate	Hoane, Akstulewicz et al., 2003
VCP													
Lateral Left Pulsion	Motor	1	10	5	severe	Lateral FPI	3.56		1.36 – 5.77	17	4	low	Pillay et al., 2007

Cont'd

Table 3.K Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Tactile Placing	Motor	1	10	5	severe	Lateral FPI	3.18		1.14 – 5.23	15	6	low	Pillay et al., 2007
Right Lateral Pulsion	Motor	1	10	5	severe	Lateral FPI	2.37		.64 – 4.11	11	13	low	Pillay et al., 2007
Simvastatin													
Morris Water Maze	Cognitive	2	20	1,440	not specified	CCI	2.49	2.76	1.96 – 5.54	24	13	moderate /high	Lu, Qu et al., 2007; Lu, Qu, Goussev et al., 2007
Atorvastatin													
Modified NSS	Motor	1	20	1,440	not specified	CCI	2.43	-	1.12 – 3.74	11	13	high	Lu, Goussev et al., 2004
Morris Water Maze	Cognitive	3	17	1,440	not specified	CCI	1.55	1.45	.19 – 2.90	34	27	high	Lu, Qu, Goussev et al., 2007, Lu, Goussev et al., 2004; Lu, Mahmood et al., 2004
Corner Test	Motor	1	20	1,440	not specified	CCI	1.41	-	.37 – 2.45	6	32	high	Lu, Goussev et al., 2004

Cont'd

Table 3.K Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
C1-INH													
Composite Neuroscore*	Motor	2	24	10 - 60	not specified	CCI	1.30	.42	.39 – 2.27	12	35	moderate	Longhi et al., 2009
Morris Water Maze*	Cognitive	2	24	10 - 60	not specifried	CCI	.91	.61	.08 – 1.86	8	45	moderate	Longhi et al., 2009
Minocycline HCl													
Rotarod*	Motor	1	16	30	not specified	WD	1.03		-.05 – 2.11	4	45	moderate	Sanchez-Mejia et al., 2001
NSS*	Motor	1	6	30	not specified	WD	.74		-.91 – 2.39	3	57	high	Bye et al., 2007
IL-18BP													
NSS*	Motor	1	34	60	not specified	WD	1.00		.25 – 1.75	4	45	high	Yatsiv et al., 2002
COG 1410													
Forelimb Placing Test	Motor	2	14	30	not specified	CCI	.95	.39	-.17 – 2.12	9	45	moderate	Hoane, Pierce et al., 2007
Bilateral Tactile Test	Motor	1	14	30	not specified	CCI	.77		-.45 – 1.73	3	53	low	Hoane, Kaufman et al., 2009

Cont'd

Table 3.K Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Limb-Use Asymmetry	Motor	2	14	30	not specified	CCI	.67	.52	-.40 – 1.81	6	57	moderate	Hoane, Pierce et al., 2007
Morris Water Maze	Cognitive	1	14	30	not specified	CCI	.64		-.33 – 1.80	2	62	low	Hoane, Kaufman et al., 2009
Beam Walk	Motor	2	14	30	not specified	CCI	.33	.01	-.73 – 1.39	2	79	moderate	Hoane, Pierce et al., 2007
IL-10													
Composite Neuroscore	Motor	1	35	5	not specified	Lateral FPI	.59		-.10 – 1.28	2	62	high	Knoblach & Faden, 1998

Note: Lateral FPI = lateral fluid percussion injury; CCI = controlled cortical impact injury; WD = weight drop injury; NSS = Neurological Severity Score

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.L: Antidiuretics

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
V-1880 (AVP V_{1a})													
Beam Walk*	Motor	1	16	3	not specified	CCI	.78		-.22 – 1.86	3	53	high	Trabold et al., 2008
V-2381 (AVP V_2)													
Beam Walk*	Motor	1	16	3	not specified	CCI	-.13		-1.12 - .84	0	92	high	Trabold et al., 2008

Note: CCI = controlled cortical impact injury

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.M: Immunosuppressants

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Cyclosporin A													
Composite Neuroscore*	Motor	1	24	15	severe	CCI	3.02		1.64 – 4.40	14	7	high	Mbye et al., 2009
Rapamycin													
NSS*	Motor	2	13	240	not specified	WD	.75	.33	-.43 – 1.97	7	53	high	Erlich et al., 2007

Note: CCI = controlled cortical impact injury; WD = weight drop injury; NSS = Neurological Severity Score

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.N: Modulators of Free Radical Formation

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Bemithyl													
Elevated Plus Maze	Behaviour	1	20	not specified	moderate	CCI	16.49		9.83 – 23.15	82	2	moderate	Zarubina, 2003
Exploratory Activity	Behaviour	1	20	not specified	moderate	CCI	7.60		4.43 – 10.77	37	2	moderate	Zarubina, 2003
Spont. Motor Activity	Behaviour	1	20	not specified	moderate	CCI	5.54		3.12 – 7.95	27	2	moderate	Zarubina, 2003
Open Field Test	Behaviour	1	20	not specified	moderate	CCI	1.41		.35 – 2.47	6	32	moderate	Zarubina, 2003
Emotional Activity	Behaviour	1	20	not specified	moderate	CCI	1.00		-.84 – 2.84	4	45	moderate	Zarubina, 2003
DETA/NONOate													
Modified NSS	Motor	1	36	1,440	severe	CCI	3.40		2.09 – 4.71	16	5	high	Lu, Mahmood, Zhang et al., 2003
Corner Test	Motor	1	36	1,440	severe	CCI	2.53		1.45 – 3.61	12	11	high	Lu, Mahmood, Zhang et al., 2003
CDP-Choline													
Composite Neuroscore	Motor	3	16	5	moderate	CCI	1.76	1.71	1.04 – 4.19	25	23	high	Dempsey & Rao, 2003
Beam Balance	Motor	1	20	1,440	not specified	CCI	.97		.01 – 1.93	4	45	moderate	Dixon, Ma, Marion, 1997

Cont'd

Table 3.N Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Beam Walk	Motor	1	20	1,440	not specified	CCI	.62		-.29 – 1.53	2	62	moderate	Dixon, Ma, Marion, 1997
Morris Water Maze	Cognitive	1	20	1,440	not specified	CCI	.09		-.79 - .97	1	92	moderate	Dixon, Ma, Marion, 1997
PBN													
Combined Neuroscore	Motor	1	17	30	moderate	Lateral FPI	1.66		.47 – 2.85	7	25	highest	Marklund, Clausen et al., 2001
Inclined Plane Test	Motor	1	17	30	moderate	Lateral FPI	.58		-.40 – 1.56	2	62	highest	Marklund, Clausen et al., 2001
Grip Test*	Motor	7	42	5	not specified	WD	.53	.32	-.06 – 1.20	18	67	high	Mesenge, Margaill et al., 1998
B2													
Tactile Removal Test	Motor	1	15	15	not specified	CCI	1.60		.36 – 2.84	7	27	high	Hoane, Wolyniak et al., 2005
Bilateral Tactile Test	Motor	1	12	60	not specified	CCI	1.14		-.12 – 2.40	5	41	moderate	Barbre & Hoane, 2006
Morris Water Maze	Cognitive	1	15	15	not specified	CCI	.66		-.40 – 1.72	2	57	high	Hoane, Wolyniak et al., 2005

Cont'd

Table 3.N Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Fine Motor Test	Motor	1	12	60	not specified	CCI	.38		-.77 – 1.53	1	73	moderate	Barbre & Hoane, 2006
DMSO													
Grip Test*	Motor	1	16	5	moderate	WD	1.27		.15 – 2.40	5	35	high	De la Torre, 1995
Murine IgG													
Composite Neuroscore	Motor	1	20	60	moderate	Lateral FPI	1.23		.22 – 2.23	5	38	high	Knoblach & Faden, 2002
Anti-ICAM													
Composite Neuroscore	Motor	1	24	60	moderate	Lateral FPI	1.19		.27 – 2.12	5	38	high	Knoblach & Faden, 2002
L-NIL													
Global Neuroscore	Motor	1	40	360	not specified	Lateral FPI	1.19		.48 – 1.91	5	38	high	Louin et al., 2006
Inosine													
Staircase Test	Motor	1	16	5	not specified	CCI	1.15		.04 – 2.25	5	38	moderate	Smith et al., 2007

Cont'd

Table 3.N Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Ladder Walking	Motor	1	16	5	not specified	CCI	.72		-.32 – 1.76	3	57	moderate	Smith et al., 2007
Cylinder Test	Motor	1	16	5	not specified	CCI	.14		-.85 – 1.13	0	92	moderate	Smith et al., 2007
1400W													
Global Neuroscore	Motor	2	28	5-360	not specified	Lateral FPI	.98	.42	.20 – 1.88	9	45	high	Louin et al., 2006
AG													
Global Neuroscore	Motor	1	36	360	not specified	Lateral FPI	.74		.04 – 1.43	3	57	high	Louin et al., 2006
7-NI													
Grip Test*	Motor	1	39	5	moderate	WD	.71		.04 – 1.37	3	57	high	Mesenge et al., 1996
S-PBN													
Combined Neuroscore	Motor	1	15	30	moderate	Lateral FPI	.65		-.41 – 1.71	2	57	highest	Marklund, Clausen et al., 2001
Inclined Plane Test	Motor	1	15	30	moderate	Lateral FPI	.46		-.58 – 1.49	1	67	highest	Marklund, Clausen et al., 2001

Cont'd

Table 3.N Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
L-NAME													
Grip Test*	Motor	2	31	5-120	moderate	WD	.61	.67	-.09 – 1.43	5	62	high	Messenge et al., 1996
Pen ME													
Grip Test*	Motor	4	65	5	severe	WD	-.50	.06	-1.01 - .00	9	67	high	Hall et al., 1999
Melatonin													
Grip Test*	Motor	6	29	5-60	not specified	WD	.26	.42	-.47 – 1.03	7	79	high	Mesenge et al., 1998

Note: CCI = controlled cortical impact injury; Lateral FPI = lateral fluid percussion injury; WD = weight drop injury; Spont. Motor Activity = Spontaneous Motor Activity; NSS = Neurological Severity Score

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.O: Steroids

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Raloxifene													
Adhesive Removal Test	Motor	1	16	15	not specified	CCI	1.14		.04 – 2.24	5	41	high	Kokiko et al., 2006
Morris Water Maze	Cognitive	1	16	15	not specified	CCI	.75		-.30 – 1.80	3	53	high	Kokiko et al., 2006
Locomotor Placing Test	Motor	1	16	15	not specified	CCI	.32		-.67 – 1.31	1	79	high	Kokiko et al., 2006
Progesterone													
Morris Water Maze	Cognitive	3	17	1,440	not specified	CCI	.12	.48	-.87 – 1.11	1	92	high	Goss et al., 2003
Elevated Plus Maze	Behaviour	3	17	1,440	not specified	CCI	.09	.35	-.90 – 1.08	0	92	high	Goss et al., 2003

Note: CCI = controlled cortical impact injury

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.P: Modulators of Amino Acid Activity

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
MgCl + B2													
Bilateral Tactile Test	Motor	1	12	60	not specified	CCI	15.64		7.99 – 23.29	77	2	moderate	Barbre & Hoane, 2006
Fine Motor Test	Motor	1	12	60	not specified	CCI	-.36		-1.50 - .78	1	73	moderate	Barbre & Hoane, 2006
MgSO													
Rotarod	Motor	2	14	30	severe	WD	1.81	.69	.56 – 3.37	17	23	high	Heath & Vink, 1998b, 1999
Open Field Test	Behaviour	1	32	30	not specified	WD	1.14		.35 – 1.93	5	41	moderate	Fromm et al., 2004
Morris Water Maze	Cognitive	1	21	15	not specified	Lateral FPI	-.28		-1.15 - .59	0	79	high	Browne et al., 2004
CP-98,113													
Morris Water Maze	Cognitive	1	23	15	moderate	Lateral FPI	1.66		.63 – 2.69	7	25	high	Okiyama, Smith et al., 1998
Composite Neuroscore	Motor	1	22	15	moderate	Lateral FPI	.94		.03 – 1.85	4	45	high	Okiyama, Smith et al., 1998

Cont'd

Table 3.P Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
HU-211													
NSS	Motor	2	16	240-360	not specified	WD	1.60	.75	.44 – 2.92	15	27	high	Shohami, Novikov et al., 1995
Morris Water Maze	Cognitive	1	22	60	not specified	WD	1.53		.51 – 2.56	7	29	high	Shohami, Novikov et al., 1995
MgCl													
Bilateral Tactile Test	Motor	1	12	60	not specified	CCI	1.43		.10 – 2.76	6	32	moderate	Barbre & Hoane, 2006
Composite Neuroscore	Motor	1	28	60	moderate	Lateral FPI	1.34		.46 – 2.21	6	35	high	Bareyre et al., 1999
Tactile Removal Test	Motor	1	20	15	not specified	CCI	1.03		.06 – 2.00	4	41	moderate	Hoane, 2005
Morris Water Maze	Cognitive	1	20	15	not specified	CCI	.62		-.32 – 1.56	2	62	moderate	Hoane, 2005
Fine Motor Test	Motor	1	12	60	not specified	CCI	-.25		-1.39 - .89	0	79	moderate	Barbre & Hoane, 2006
½ MgCl + ½ B2													
Bilateral Tactile Test	Motor	1	12	60	not specified	CCI	1.24		-.04 – 2.52	5	38	moderate	Barbre & Hoane, 2006

Cont'd

Table 3.P Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Fine Motor Test	Motor	1	12	60	not specified	CCI	-.11		-1.24 – 1.02	1	92	moderate	Barbre & Hoane, 2006
Dextrorphan													
Composite Neuroscore	Motor	1	22	30	not specified	Lateral FPI	1.20		.25 – 2.15	5	38	high	Faden, 1993
CP-101,606													
Morris Water Maze	Cognitive	1	24	15	moderate	Lateral FPI	1.07		.17 – 1.96	4	41	high	Okiyama, Smith et al., 1997
CP-101,581													
Morris Water Maze	Cognitive	1	25	15	moderate	Lateral FPI	1.04		.17 – 1.91	4	45	high	Okiyama, Smith et al., 1997
DCS													
Morris Water Maze	Cognitive	2	17	1,440	moderate	Lateral FPI	1.03	.86	.06 – 2.29	9	45	high	Temple & Hamm, 1996
Object Recognition Test*	Cognitive	1	18	1,440	not specified	WD	.87		-.12 – 1.87	3	48	high	Yaka et al., 2007

Cont'd

Table 3.P Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Aniracetam													
Morris Water Maze	Cognitive	2	18	1,440	moderate	Central FPI	.91	.13	-.09 – 1.92	8	48	high	Baranova et al., 2006
Eliprodil													
Freezing Response	Cognitive	1	18	15	not specified	Lateral FPI	.88		-.11 – 1.87	3	48	high	Hogg et al., 1998
MDL 26,479													
Morris Water Maze	Cognitive	2	20	15,840	moderate	Central FPI	-.61	.00	-1.52 - .30	5	62	high	O'Dell & Hamm, 1995
Ketamine													
NSS	Motor	1	22	60	not specified	WD	.53		-.33 – 1.39	2	67	high	Shapira, Artru et al., 1992
NPS 1506													
Morris Water Maze	Cognitive	2	26	10-15	moderate	Lateral FPI	.35	.89	-.55 – 1.09	3	73	high	Leoni et al., 2000; Browne et al., 2004

Note: CCI = controlled cortical injury; WD = weight drop injury; Lateral FPI = lateral fluid percussion injury; Central FPI = central fluid percussion injury; NSS = Neurological Severity Score

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.Q: Growth Factors

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
EPO +BrdU												
Morris Water Maze	Cognitive	1	12	1,440	not specified	CCI	2.38	.77 – 3.99	11	13	high	Lu, Mahmood, Qu et al., 2005
EPO												
Object Recognition*	Cognitive	1	36	60	not specified	WD	1.41	.60 – 2.22	6	32	high	Yatsiv et al., 2005
NSS*	Motor	1	36	60	not specified	WD	.97	.25 – 1.69	4	45	high	Yatsiv et al., 2005
NGF											high	
Morris Water Maze	Cognitive	1	24	1,440	moderate	Lateral FPI	1.07	.18 – 1.96	4	41		Sinson et al., 1997
Morris Water Maze	Motor	1	20	5	not specified	CCI	-.16	-1.03 - .72	0	85	high	Dixon, Flinn et al, 1997
mAB 7B12												
Morris Water Maze	Cognitive	1	24	1,440	moderate	Lateral FPI	.61	-.22 – 1.44	2	62	high	Marklund, Bareyre et al., 2007
Composite Neuroscore	Motor	1	24	1,440	moderate	Lateral FPI	-.34	-1.15 - .47	1	79	high	Marklund, Bareyre et al., 2007

Note: Lateral FPI = lateral fluid percussion injury; CCI = controlled cortical impact injury

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Table 3.R: Other

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
Pyracetum													
Elevated Plus Maze	Behaviour	1	20	not specified	moderate	CCI	8.41		4.93 – 11.90	41	2	moderate	Zarubina, 2003
Exploratory Activity	Behaviour	1	20	not specified	moderate	CCI	1.83		.69 – 2.98	8	23	moderate	Zarubina, 2003
Spont. Motor Activity	Behaviour	1	20	not specified	moderate	CCI	1.07		.09 – 2.04	4	41	moderate	Zarubina, 2003
Open Field Test	Behaviour	1	20	not specified	moderate	CCI	.34		-.55 – 1.23	1	79	moderate	Zarubina, 2003
Emotional Activity	Behaviour	1	20	not specified	moderate	CCI	.17		-.73 – 1.07	0	85	moderate	Zarubina, 2003
FDP + DMSO													
Grip Test*	Motor	1	16	5	moderate	WD	4.78		2.47 – 7.08	23	2	high	De al Torre, 1995
NIM811													
Composite Neuroscore*	Motor	1	24	15	severe	CCI	3.85		2.21 – 5.49	18	3	high	Mbye et al., 2009
FTS													
NSS*	Motor	1	20	60	moderate	WD	2.28		1.01 – 3.55	10	16	high	Shohami, Yatsiv et al., 2003

Cont'd

Table 3.R Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
NSS	Motor	1	14	60	moderate	WD	.88		-.24 – 2.00	3	48	highest	Marciano, et al., 2007
GTSs													
Rotarod	Motor	2	12	5	not specified	CCI	-1.91	1.36	-3.88 - -.66	18	21	high	Ji, Kim, Park et al., 2005
Posture Reflex	Motor	2	12	5	not specified	CCI	.78	.43	-.40 – 2.01	7	53	high	Ji, Kim, Park et al., 2005
Beam Balance	Motor	2	12	5	not specified	CCI	-.44	.33	-1.60 - .71	3	73	high	Ji, Kim, Park et al., 2005
Fenofibrate													
Global Neuroscore	Motor	2	14	360	moderate	Lateral FPI	1.50	.18	.22 – 2.82	14	29	high	Besson et al., 2005
HSA													
Composite Neuroscore	Motor	1	17	15	not specified	Lateral FPI	1.47		.33 – 2.61	6	29	high	Belayev, Alsonso et al., 1999
sAPPa													
Rotarod	Motor	1	6	30	severe	WD	-1.02		-3.24 – 1.20	4	45	high	Thornton, Vink et al., 2006

Cont'd

Table 3.R Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
INO-1001													
Morris Water Maze*	Cognitive	1	22	5	moderate	CCI	.93		.02 – 1.84	4	48	high	Clark, Vagni et al., 2007
FDP													
Grip Test*	Motor	1	16	5	moderate	WD	.86		-.19 – 1.90	3	48	high	De la Torre, 1995
2-AG													
NSS*	Motor	3	20	15	not specified	WD	.79	.17	-.13 – 1.73	11	53	moderate	Panikashvili et al., 2001
Lactate													
Morris Water Maze	Motor	1	18	30	moderate	Lateral FPI	.78		-.20 – 1.76	3	53	high	Rice et al., 2002
Morris Water Maze	Cognitive	4	20	30	not specified	Lateral FPI	.39	.25	-.49 – 1.30	7	73	high	Holloway et al., 2007
Nizofenone													
Grip Test*	Motor	3	65	60	severe	WD	.45	.25	-.12 - .97	6	67	high	Hayashi et al., 1994
Levetiracetam													
Rotarod*	Motor	2	23	30	not specified	CCI	.45	.44	-.40 – 1.33	4	67	moderate	Wang et al., 2006

Cont'd

Table 3.R Cont'd

Drug and Measure	Construct	$N_{studies}$	$N_{animals}$	Injury to Treatment (minutes)	Injury Severity	Injury Model	M d_w	SD d_w	95% CIs	Nfs	OL%	Study Quality	Study Reference
OKY-046													
NSS	Motor	1	17	5	not specified	WD	-.44		-1.41 - .54	1	67	moderate	Shapira, Yadid et al., 1989
VA-045													
Water Finding Task*	Motor	8	37	30	mild	WD	.13	.42	-.53 - .81	4	92	high	Tang, Noda et al, 1997a, b
Water Finding Task*	Cognitive	4	34	30	mild	WD	.02	.36	-.67 - .70	1	100	high	Tang, Noda et al., 1997b
NBP													
Memory Task*	Cognitive	3	45	5-60	not specified	WD	.11	.07	-.48 - .70	1	92	high	Chong & Feng, 2000

Note: CCI = controlled cortical impact injury; WD = weight drop injury; Spont. Motor Activity = Spontaneous Motor Activity; NSS = Neurological Severity Score

*Findings based on a mouse model of TBI. All other findings were based on a rat model of TBI.

Chapter 4

Figure 4.1: Details of electronic database searches

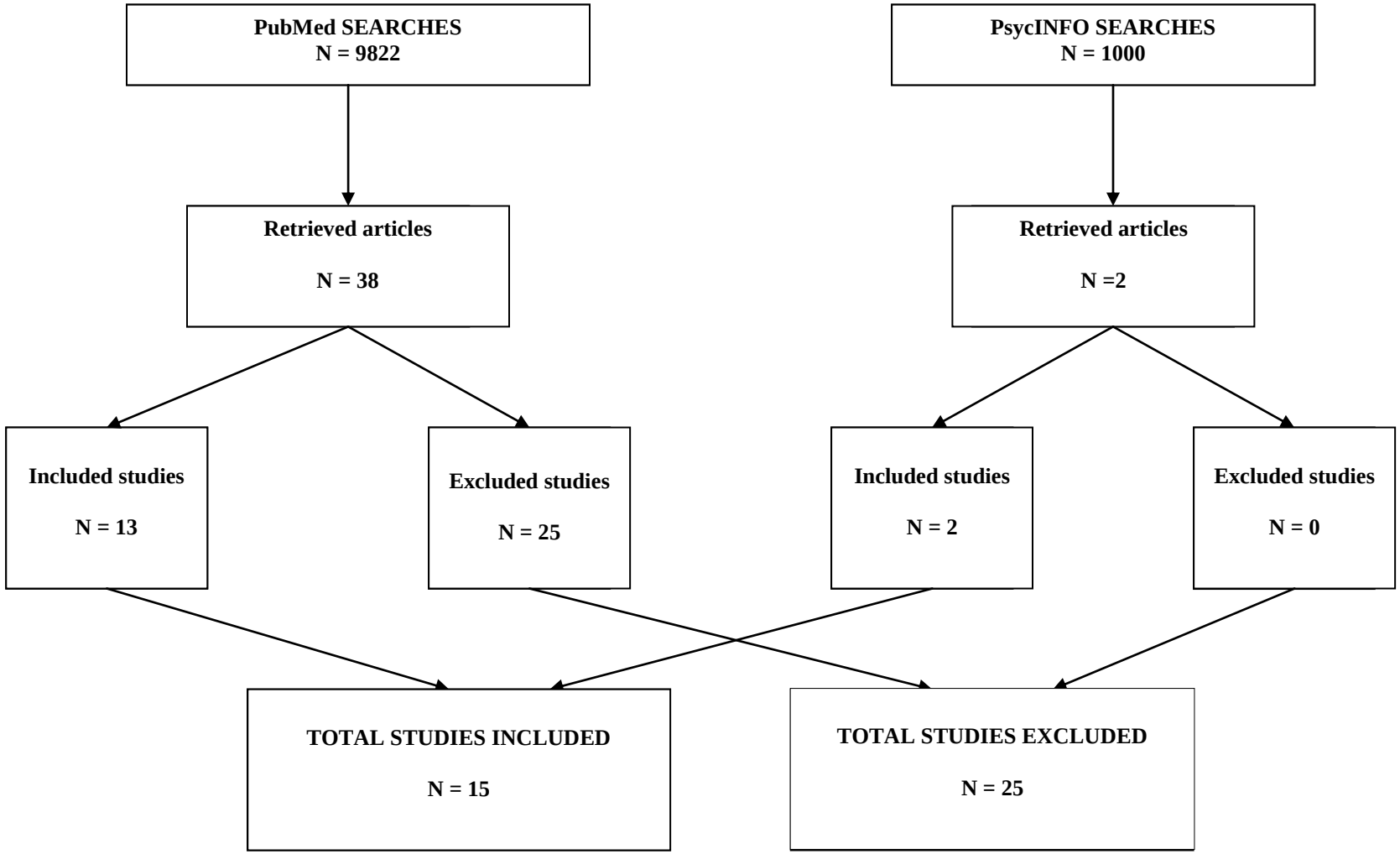

Table 4.A: Key search terms used in database searches

Traumatic brain injury	**Pharmacology**	
traumatic brain injury	pharmacology	drug therapy
TBI	pharmacological treatment	pharmacotherapy
head injury	drug treatment	drug
head injuries	magnesium or Mg	substance P
brain injury	cyclosporin A or CyA	progesterone
brain injuries	oestrogen	dexanabinol
head trauma	dexamethasone	dynorphin
concussion	methylphenidate	amitriptyline
post-concussion	phenelzine	opiate
post concussion	glutamate	calcium
post-concussion syndrome	free radical scavenger	NMDA
post concussion syndrome	treatment	

Table 4.B: Demographic data, treatment and cognitive or behavioural tests used for each study included in the human meta-analysis.

STUDY NAME	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (hours)	SEVERITY	DRUG (Category)	DRUG DOSAGE	TREATMENT DURATION	COGNITIVE/ BEHAVIOURAL TESTS
SEROTONERGIC TREATMENTS										
1. Ohman, Braakman, Legout (2001) Study 1	Independent groups	14	39.4	41.8	24	severe	**BAY X 3702** (Repinotan) Serotonin agonist	.5mg/day	7 day continuous infusion	Glasgow Outcome Scale (3 month)
1. Ohman, Braakman, Legout (2001) Study 2	Independent groups	14	35.4	41.8	24	severe	**BAY X 3702 (**Repinotan) Serotonin agonist	1.25mg/day	7 day continuous infusion	Glasgow Outcome Scale (3 month)
1. Ohman, Braakman, Legout (2001) Study 3	Independent groups	15	33.4	41.8	24	severe	**BAY X 3702** (Repinotan) Serotonin agonist	2.5mg/day	7 day continuous infusion	Glasgow Outcome Scale (3 month)
CATECHOLAMINERGIC TREATMENTS										
2. Saniova et al. (2004)	Independent groups repeated measures	41	42.12 (16.8)	43.91 (18.45)	72	severe	**Amantadine** (Symmetrel) Dopamine agonist	400mg/day	Variable (to discharge)	Glasgow Coma Scale
CALCIUM CHANNEL BLOCKERS										
3. Pillai et al. (2003)	Independent groups	50	30 (12)	29 (10)	6.1	severe	**Nimodipine** (Nimotop) Calcium channel blocker	30mg/6 hours	3 weeks (21 days)	Glasgow Outcome Scale (6 month)
4. The European Study Group on Nimodipine (1994)	Independent groups	405	36.9	35.7	8.45	severe	**Nimodipine** (Nimotop) Calcium channel blocker	1mg/hour	1 week (7 days)	Glasgow Outcome Scale (6 month)
NMDA ANTAGONISTS										
5. Yurkewicz et al. (2005)	Independent groups	198	31	31.5	8	severe	**CP-101,606** (Traxoprodil) NMDA antagonist	.75mg/kg	72 hour infusion (3 days)	Glasgow Outcome Scale (6 month); Disability Rating Scale; Cognitive Abilities Screening

Cont'd

Table 4.B Cont'd

STUDY NAME	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (hours)	SEVERITY	DRUG (Category)	DRUG DOSAGE	TREATMENT DURATION	COGNITIVE/ BEHAVIOURAL TESTS
6. Lepeintre et al. (2004) Study 1	Independent groups	11	37 (4)	27 (2)	2	severe	**GK-11** (Gacyclidine) NMDA antagonist	.01mg/kg	2 doses in one day (1 day)	Glasgow Outcome Scale (3 month)
6. Lepeintre et al. (2004) Study 2	Independent groups	13	31 (4)	27 (2)	2	severe	**GK-11** (Gacyclidine) NMDA antagonist	.02mg/kg	2 doses in one day (1 day)	Glasgow Outcome Scale (3 month)
6. Lepeintre et al. (2004) Study 3	Independent groups	12	36 (4)	27 (2)	2	severe	**GK-11** (Gacyclidine) NMDA antagonist	.04mg/kg	2 doses in one day (1 day)	Glasgow Outcome Scale (3 month)
STEROIDS										
7. Crash Trial Collaborators (2005)	Independent groups	4800	-	-	8 (max)	mild/moderate/severe	**Methylprednisolone** (Medrol) Corticosteroid	2g in 1 hour	48 hour infusion (2 days)	Glasgow Outcome Scale (6 month)
8. Saul et al. (1981)	Independent groups	50	32	30	72 (Min)	severe	**Methylprednisolone** (Medrol) Corticosteroid	5mg/day	-	Glasgow Outcome Scale (6 month)
PEPTIDE TREATMENTS										
9. Narotam et al. (1998)	Independent groups repeated measures	11	27 (3.6)	26 (3.8)	51.5	mild/moderate	**CP-0127** (Bradycor) Peptide	3mg/kg/min	7 days	Glasgow Coma Scale
10. Marmarou et al. (1999)	Independent groups	66	30 (12)	34 (14)	10	severe	**CP-0127** (Bradycor) Peptide	3Ug/kg/min	5 days	Glasgow Outcome Scale (3 & 6 month)
11. Marmarou, Guy et al. (2005) Study 1	Independent groups	10	39.1 (13)	33.5 (15)	10	severe	**LF 16-0687Ms** (Anatibant) Peptide	3.75 mg	Single injection	Glasgow Outcome Scale (3 & 6 month)
11. Marmarou, Guy et al. (2005) Study 2	Independent groups	10	31.2 (17)	33.5 (15)	10	severe	**LF 16-0687Ms** (Anatibant) Peptide	22.5 mg	Single injection	Glasgow Outcome Scale (3 & 6 month)

Cont'd

Table 4.B Cont'd

STUDY NAME	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (hours)	SEVERITY	DRUG (Category)	DRUG DOSAGE	TREATMENT DURATION	COGNITIVE/ BEHAVIOURAL TESTS
12. Filipova et al. (1989)	Independent groups repeated measures	9	41	28	28 (mid)	mild	**Desmospressin** – (DDAVP) Peptide	20mg/day	4.3 days	Paced Auditory Serial Addition Test (I & II); Story Memory
CANNABINOIDS										
13. Knoller et al. (2002)	Independent groups	30	29 (12)	31 (13)	4.95	severe	**Dexanabinol** Cannabinoid	48mg/day	Single dose (1 day)	Glasgow Outcome Scale (3 month)
14. Maas et al. (2006)	Independent groups	428	-	-	6 (max)	severe	**Dexanabinol** Cannabinoid	150mg/day	Single intravenous injection (1 day)	Extended Glasgow Outcome Scale (best, moderate and worst progrnostic band) (3 & 6 month)
FREE RADICAL SCAVENGERS										
15. Muizellar et al (1993) Study 1	Independent groups	26	27 (9.7)	25.4 (7.6)	3.4	severe	**PEG-SOD** (Pegorgotein) Oxygen radical scavenger	2,000U/kg	Single injection (1 day)	Glasgow Outcome Scale (3 & 6 month)
15. Muizellar et al. (1993) Study 2	Independent groups	25	32.6 (14.7)	25.4 (7.6)	3.65	severe	**PEG-SOD** (Pegorgotein) Oxygen radical scavenger	5,000U/kg	Single injection (1 day)	Glasgow Outcome Scale (3 & 6 month)
15. Muizellar et al. (1993) Study 3	Independent groups	27	34.2 (17.9)	25.4 (7.6)	4.05	severe	**PEG-SOD** (Pegorgotein) Oxygen radical scavenger	10.000U/kg	Single injection (1 day)	Glasgow Outcome Scale (3 & 6 month)

Note: SSRI = Selective serotonin reuptake inhibitor; SNRI = Seratonin Noradrenaline reuptake inh

Table 4.C: Chemical group, pharmacological category and method of action of drugs.

Chemical Group	**Pharmacological Category**	**Method of Action**	**Drug (Brand Name)**
Serotonergic	Antidepressant	Serotonin Agonist	BAY X 3702 (Repinotan)
Catecholamine	Anti-Parkinsonian	Dopamine Agonist	Amantadine (Symmetrel)
Calcium Channel Blocker	Anti-vasospasm	Modulator of ion homeostasis	Nimodipine (Nimotop)
NMDA antagonist	Anticonvulsant	Amino Acid	CP-101,606 (Traxoprodil) GK-11 (Gacyclidine)
Steroid	Anti-inflammatory	Corticosteroid	Methylprednisolone (Medrol)
Peptide	Anti-inflammatory/ Antiviral	Bradykinin antagonist (Peptide)	CP-0127 (Bradycor) LF 16-0687Ms (Anatibant)
	Anti-diuretic	Peptide	Desmopressin (DDAVP/Stimate)
Cannabinoid	Anti-inflammatory	Cannabinoid	Dexanabinol
Free Radical Scavenger	Antioxidant	Oxide Scavenger	PEG-SOD (Pegorgotein)

Note: PEG-SOD = polyethyleglycol-conjugated superoxide dismutase; NMDA = n-methyl-D-aspartate; MAOI = monoamine oxidase inhibitor; SSRI = Selective serotonin reuptake inhibitor; SNRI = Serotonin noradrenaline reuptake inhibitor; CNS = Central Nervous System Stimulant.

Table 4.D: Methodological quality rating system

Question		Score
1	Demographically matched control group or condition provided	1
2	The control group is matched to the treatment group on initial performance	1
3	Patients were randomly allocated to groups	1
4	The method of randomization was described	1
5	The cognitive or behavioural test is clearly described (or a reference provided)	1
6	The scores for each measure are specified (i.e. error, accuracy, speed)	1
7	The age of the participants is specified (M/SD/Range)	1
8	The severity of injury is specified	1
9	The measure/s of injury severity are provided (i.e. GCS, PTA, LOC)	1
10	The gender of participants is specified	1
11	Relevant premorbid demographic statistics are reported (e.g., education, IQ)	1
12	The initial sample size for each group is specified	1
13	The time from injury to treatment is specified	1
14	The drugs dosage is specified	1
15	Significant test statistics are provided that would enable the calculation of an effect size (Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value)	1
16	The N for each group on each testing occasion is reported	1
17	Non-significant test statistics are reported that would enable the calculation of an effect size (Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value)	1
18	Group allocation is blinded to the assessor	1
19	Group allocation is blinded to the patient	1
20	N lost to follow-up is reported	1
	TOTAL SCORE / 20	

Note: M = Mean score; SD = Standard deviation of score; GCS = Glasgow Coma Scale; PTA = duration of post-traumatic amnesia; LOC = duration of loss of consciousness; N = number of participants; IQ = intelligence quotient.

Appendix 4.A: Reference list for all studies included in the meta-analysis

CRASH Trial Collaborators. (2005). Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury - outcomes at 6 months. *Lancet, 365*, 1957-1959.

Filipova, M., Jung, M., & Krejcova, H. (1989). Clinical efficacy of 1-Desamino-8-D-Arginine-Vasopressin (DDAVP) in short-term recovery from minor head injury. *Human Psychopharmacology, 4*, 47-50.

Knoller, N., Levi, L., Shoshan, I., Reichenthal, E., Razon, N., Rappaport, Z. H., et al. (2002). Dexanabinol (HU-211) in the treatment of severe closed head injury: A randomized, placebo-controlled, phase II clinical trial. *Critical Care Medicine, 30*(3), 548-554.

Lepeintre, J.-F., D'Arbigny, P., Mathe, J.-F., Vigue, B., Loubert, G., Delcour, J., et al. (2004). Neuroprotective effect of gacyclidine: A multicenter double-blind pilot trial in patients with acute traumatic brain injury. *Neurochirurgie, 50*(2-3), 83-95.

Maas, A. I. R., Murray, G., Henney, H., Kassem, N., Legrand, V., Mangelus, M., et al. (2006). Efficacy and safety of dexanabinol in severe traumatic brain injury: Results of a phase III randomised, placebo-controlled, clinical trial. *Lancet, 5*, 38-45.

Marmarou, A., Guy, M., Murphey, L., Roy, F., Layani, L., Combal, J.-P., et al. (2005). A single dose, three-arm, placebo-controlled, phase 1 study of the bradykinin B2 receptor antagonist anatibant (LF16-0687Ms) in patients with severe traumatic brain injury. *Journal of Neurotrauma, 22*(12), 1444-1455.

Marmarou, A., Nichols, J., Burgess, J., Newell, D., Troha, J., Burnham, D., et al. (1999). Effects of the bradykinin antagonist bradycor (deltibant, CP-1027) in severe

traumatic brain injury: Results of a multi-center, randomized, placebo-controlled trial. *Journal of Neurotrauma, 16*(6), 431-444.

Muizelaar, J. P., Marmarou, A., Young, H. F., Choi, S. C., Wolf, A., Schneider, R. L., et al. (1993). Improving the outcome of severe head injury with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase: a phase II trial. *Journal of Neurosurgery, 78*, 375-382.

Narotam, P. K., Rodell, T. C., Nadvi, S. S., Bhoola, K. D., Troha, J. M., Parbhoosingh, R., et al. (1998). Traumatic brain contusions: A clinical role for the kinin antagonist CP-0127. *Acta Neurochirurgica, 140*, 793-803.

Ohman, J., Braakman, R., & Legout, V. (2001). Repinotan (BAY X 3702): A 5HT1A agonist in traumatically brain injured patients. *Journal of Neurotrauma, 18*(12), 1313-1321.

Pillai, S. V., Kolluri, V. R. S., Mohanty, A., & Chandramouli, B. A. (2003). Evaluation of nimodipine in the treatment of severe diffuse head injury: A double-blind placebo-controlled trial. *Neurology India, 51*(3), 361-363.

Saniova, B., Drobny, M., Kneslova, L., & Minarik, M. (2004). The outcome of patients with severe head injuries treated with amantadine sulphate. *Journal of Neural Transmission, 111*, 511-514.

Saul, T. G., Ducker, T. B., Salcman, M., & Carro, E. (1981). Steroids in severe head injury: A prospective randomized clinical trial. *Journal of Neurosurgery, 54*, 596-600.

The European Study Group on Nimodipine in Severe Head Injury. (1994). A multicenter trial of the efficacy of nimodipine on outcome after severe head injury. *Journal of Neurosurgery, 80*, 797-804.

Yurkewicz, L., Weaver, J., Bullock, M. R., & Marshall, L. F. (2005). The effect of the selective NMDA receptor antagonis traxoprodil in the treatment of traumatic brain injury. *Journal of Neurotrauma, 22*(12), 1428-1443.

Chapter 5

Table 5.A: Key search terms used in database searches

Traumatic brain injury	**Pharmacology**	
traumatic brain injury	pharmacology	drug therapy
TBI	pharmacological treatment	pharmacotherapy
head injury	drug treatment	drug
head injuries	magnesium or Mg	substance P
brain injury	cyclosporin A or CyA	progesterone
brain injuries	oestrogen	dexanabinol
head trauma	dexamethasone	dynorphin
concussion	methylphenidate	amitriptyline
post-concussion	phenelzine	opiate
post concussion	glutamate	calcium
post-concussion syndrome	free radical scavenger	NMDA
post concussion syndrome	treatment	

Figure 5.1: Details of electronic database searches

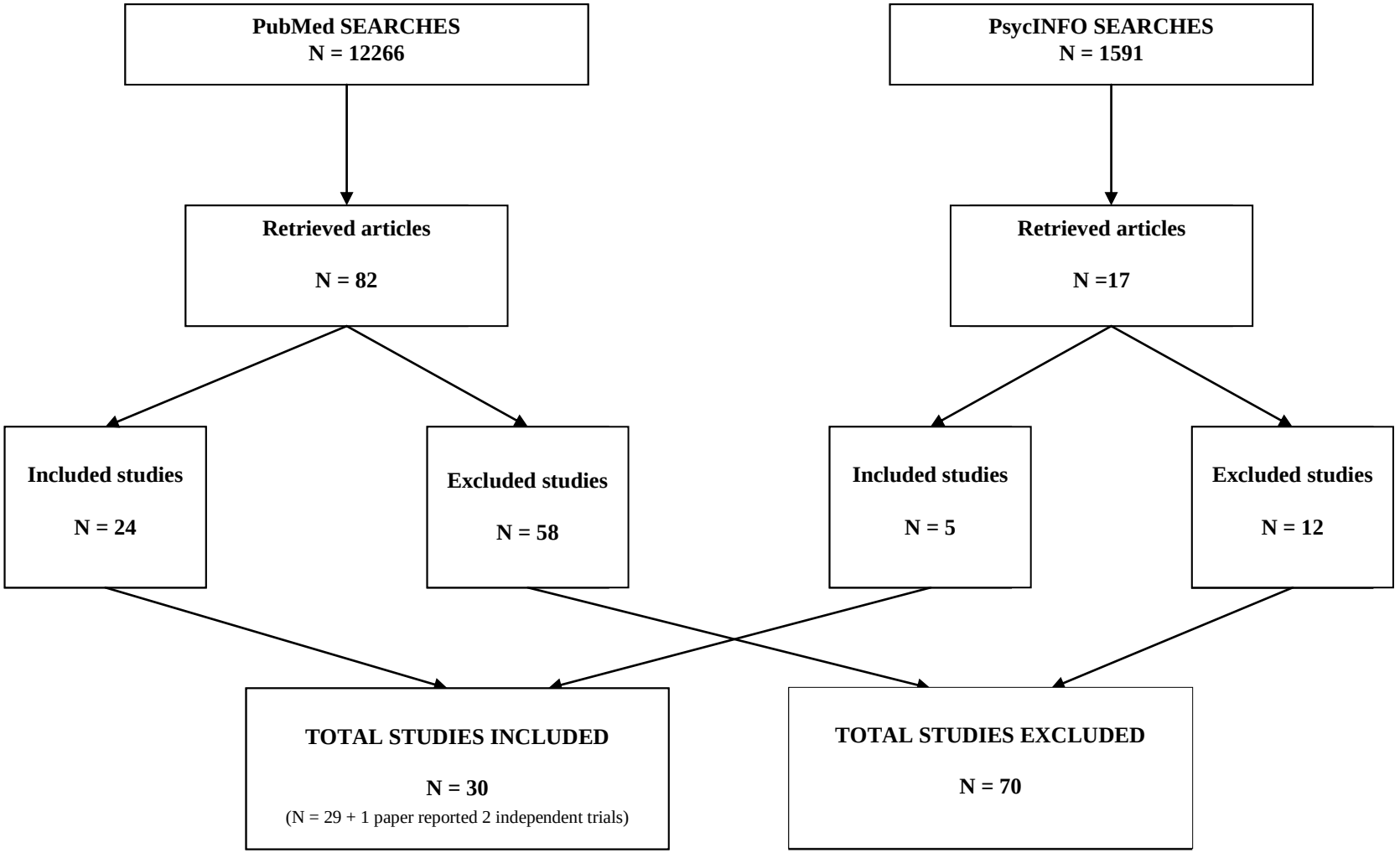

Table 5.B : Demographic data, treatment and cognitive or behavioural tests used for each study included in the meta-analysis.

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
SEROTONERGIC TREATMENTS											
POST-ACUTE											
Perino et al., 2001	*Open-label* Repeated measures	20	29.10	-	84 (8 – 144)	severe	**Citalopram** (Ciprimil) SSRI & **Carbamazepine** (Tegretol) Sodium Channel Blocker	10mg – 20mg/day 100mg/day	3 months (90 days)	6.7	Brief Psychiatric Rating Scale; Clinical Global Impression Scale
Dinan & Mobayed, 1992	*Open-label* Repeated measures	13	30 (7)	-	36 (mid) (24 – 48)	mild	**Amitriptyline** (Tryptanol) Tricyclic antidepressant	100mg – 250mg/day	6 weeks (42 days)	6.9	Hamilton Rating Scale for Depression
Saran, 1988	*Open-label* Repeated measures	10	42	-	30 (mid) (16 – 44)	mild	**Amitriptyline** (Tryptanol) Tricyclic antidepressant **Phenelzine** (Nardil) Monoamine oxidase inhibitor	100mg – 300mg/day (max) 45mg/day	4 weeks (28 days)	7.2	Hamilton Rating Scale for Depression Hamilton Rating Scale for Depression
Wroblewski et al., 1996	*RCT* *(double-blinded)* Independent groups repeated measures	3	36 (8)	30 (9)	60 (mid) (24 – 96)	severe	**Desipramine** (Norpramin) Tricyclic antidepressant	150mg – 300mg/day	4 weeks	8.0	Affect/Mood Scale
MIXED											
Kanetani et al., 2003	*Open-label* Repeated measures	10	-	-	22 (3 – 73)	mild/ moderate	**Milnacipran** (Ixel) SNRI	30mg – 150mg/day	6 weeks (42 days)	7.8	Mini-mental State Exam; Hamilton Rating Scale for Depression

Cont'd

Table 5.B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
Lee et al., 2005 (Study 2)	*RCT (double-blinded)* Independent groups repeated measures	10	33.6 (12.3)	35.5 (7.2)	4 (>2 < 52)	mild/ moderate	**Sertraline** (Zoloft) SSRI	25mg – 100mg/day	4 weeks (28 days)	9.5	Beck Depression Inventory; Hamilton Rating Scale for Depression, Rivermead Post-concussion Symptoms Questionnaire; SmithKline Beecham Quality of Life Scale; Critical Flicker Fusion Threshold; Choice Reaction Time; Compensatory Tracking Task (tracking and peripheral); Mental Arithmetic Test; Sternberg Memory Scanning Task, Digit Symbol Substitution Test; Mini-mental State Exam
CATECHOLAMINE TREATMENTS											
POST-ACUTE											
Kim et al., 2006	*RCT (double-blinded)* Independent groups repeated measures	9	30.10 (11.5)	38.3 (9.8)	142 (> 24)	-	**Methylphenidate** (Ritalin) Stimulant	20mg/day	Single dose (1 day)	7.0	Modified Posner Paradigm; Working Memory Task
Mooney & Haas, 1993	*RCT (single-blinded)* Independent groups repeated measures	19	-	-	108 (mid) (> 24)	severe	**Methylphenidate** (Ritalin) Stimulant	30mg/day	6 weeks (42 days)	8.3	State & Trait Anger; Profile of Mood States; Katz Adjustment Scale (belligerence, psychopathology); Organic Signs & Symptoms Inventory
Speech et al., 1993	*RCT (double-blinded)* Cross-over	12	27.58	-	208 (56 – 432)	moderate/ severe	**Methylphenidate** (Ritalin) Stimulant	.30mg/kg	1 week (7 days)	8.5	WAIS Digit Symbol; Stroop Interference; Choice reaction time; Sternberg Memory Scanning Task; Selective Reminding Test; Serial Digit Learning; Gordon Diagnostic System; Digit Span

Cont'd

Table 5.B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
Whyte et al., 1997	*RCT (double-blinded)* Cross-over	19	30.8	-	74 (5 – 464)	mild/ moderate/ severe	**Methylphenidate** (Ritalin) Stimulant	.50mg/kg/ day	6 days (non-consecutive – drug given 90 minutes before task)	9.0	Distraction Task; Phasic Arousal Task; Choice reaction time; Behavioural Inattention Task; Visual go/no-go Task
Kraus et al., 2005	*Open-label* Repeated measures	22	36 (11.8)	-	270 (24 – 960)	mild/ moderate/ severe	**Amantadine** (Symmetrel) Stimulates dopamine release	100mg – 400mg/day	3 months (90 days)	8.3	Trails A & B; Controlled Oral Word Association Test; Digit Span; Californai Verbal Learning Test; Rey Osterreith Complex Figure (immediate and delayed)
Kim & Bijlani, 2006	*Open-label* Repeated measures	7	48.9 (2.4)	-	99 (> 12)	mild/ moderate/ severe	**Quetiapine** (Seroquel) Dopamine antagonist	25mg – 300mg/day	6 weeks (42 days)	6.1	Clinical Global Impression Scale; The Overt Aggression Scale-Modified; Neurobehavioral Functioning Inventory (Aggression); Repeatable Battery for the Assessment of Neuropsychological Status
Noe et al., 2007	*Retrospective Open-label* Repeated measures	5	27 (10)	-	8 (5 – 10)	severe	**Ziprasidone** (Geodon) Dopamine antagonist	20mg – 80mg/day	2 weeks	8.9	Agitated Behaviour Scale
Fridman et al., 2010	*Open-label* Repeated measures	8	23 (4)	-	10 (6 – 15)	severe	**Apomorphine** (Apokyn) Dopamine agonist	2mg – 8mg/hour	84 – 180 days	8.0	Coma Near-Coma Scale, Disability Rating Scale

Cont'd

Table 5.B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
MIXED											
Lee et al., 2005 (Study 1)	*RCT (double-blinded)* Independent groups repeated measures	10	35.3 (8)	35.5 (7.2)	5 (> 2 < 52)	mild/ moderate	**Methylphenidate** (Ritalin) Stimulant	5mg – 20mg/day	4 weeks (28 days)	9.5	Beck Depression Inventory; Hamilton Rating Scale for Depression, Rivermead Post-concussion Symptoms Questionnaire; SmithKline Beecham Quality of Life Scale; Critical Flicker Fusion Threshold; Choice Reaction Time; Compensatory Tracking Task (tracking and peripheral); Mental Arithmetic Test; Sternberg Memory Scanning Task; Digit Symbol Substitution Test; Mini-mental State Exam.
Willmott & Ponsford, 2009	*RCT (double blinded)* Cross-over	40	26.3 (9)	-	34 (mid) (<2 – 66)	moderate/ severe	**Methylphenidate** (Ritalin) Stimulant	15mg – 30mg/ twice daily	2 weeks (14 days)	9.5	Ruff 2 and 7 Selective Attention Test; Selective Attention Task; 4 Choice Reaction Time Task; Sustained Attention to Response Task; Symbol Digit Modalities Test; Letter Number Sequencing; Rating Scale for Attentional Behaviour
Meythaler et al., 2002	*RCT (double-blinded)* Independent groups repeated measures	15	-	-	4 (mid) (< 1 – 6)	moderate/ severe	**Amantadine** (Symmetrel) Stimulates dopamine release	200mg/day	6 weeks (42 days)	7.0	Mini-mental State Exam; Disability Rating Scale; Glasgow Outcome Scale; Functional Independence Measure

Cont'd

Table 5.B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
CHOLINERGIC TREATMENTS											
POST-ACUTE											
Kaye et al., 2003	*Open-label* Repeated measures	10	41	-	63 (48 – 240)	mild/ moderate/ severe	**Donepezil** (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	8 weeks (56 days)	6.4	Memory Assessment Scale
Khateb et al., 2005	*Open-label* Repeated measures	10	43 (8)	-	180 (> 24)	moderate/ severe	**Donepezil** (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	3 months (90 days)	8.9	Dysexecutive Questionnaire; Hospital Anxiety & Depression Scale; Divided attention (reaction time – dual task); Visual & Verbal Span; Revy Auditory Verbal Memory Test (recall & learning); Trail Making Test A & B; Stroop (errors, interference, reading, naming); Figural, Phonological & Categorical Fluency
Masanic et al., 2001	*Open-label* Repeated measures	4	29.5	-	162 (mid) (140 – 184)	severe	**Donepezil** (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	3 months (90 days)	7.8	Rey Auditory Verbal Learning Test (learning and recall); Complex Figure Test; Rivermead Behavioural Memory Test
Zhang et al., 2004	*RCT (double-blinded)* Independent groups repeated measures	9	33 (6)	31 (6)	18 (8 –44)	Mild/ moderate/ severe	**Donepezil** (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	10 weeks (70 days)	10.0	Weschler Memory Scale (logical memory – immediate recall; visual reproduction – immediate recall); PASAT (2.4; 2.0; 1.6; 1.2s)

Cont'd

Table 5.B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
Kim et al., 2009	*RCT (blinding not reported)* Independent groups repeated measures	13	42 (4)	40 (3)	21 (4 – 36)	not specified	**Donepezil** (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	6 weeks (42 days)	6.5	Mini Mental State Exam, Wechsler Memory Scale, Boston Naming Test, Colored Progressive Matrices.
Levin et al., 1986	*RCT (double-blinded)* Independent groups repeated measures,	8	26.5 (5.8)	25.2 (5.8)	20 (6 – 49)	Moderate/ severe	**Physostigmine** (Eserine Sulphate) Acetylcholinesterase inhibitor & **Lecithin** Cholinesterase precursor	3mg – 4.5mg/day	1 week (7 days)	9.5	Continuous Performance Test; Digit Span; Digit Cancellation; Visual Recognition Memory; Selective Reminding Test (consistent long term recall)
MIXED											
Walker et al., 2004	*Retrospective Open-label (matched, non-treated controls)* Independent groups	10	32.6	31.8	5 (2)injury to rehab (treatment administered between 3 – 84 days after rehab admission)	Moderate/ severe	**Donepezil** (Aricept) Acetylcholinesterase inhibitor	5mg – 10mg/day	1 month (mean) (28 days)	7.0	Functional Independence Measure (total score, change scores, efficiency scores)
SODIUM CHANNEL BLOCKERS											
POST-ACUTE											
Azouvi et al., 1999	*Open-label* Repeated measures	10	33.7 (14.8)	-	58 (11 – 88)	severe	**Carbamazepine** (Tegretol) Sodium Channel Blocker	400-800mg/day	8 weeks (56 days)	8.1	Shortened Neurobehavioural Rating Scale; Agitated Behaviour Scale; Mini Mental State Exam; Global Neurobehavioural Rating Scale

Cont'd

Table 5.B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
Eames & Wood, 1999	*Open-label* Repeated measures	26	33.5 (1.2)	-	256 (28 – 700)	severe	**Lysine Vasopressin** Antidiuretic peptide	8units/day (2 squirts of nasal spray/day)	4 weeks (28 days)	7.2	WMS Logical Memory (immediate and delayed recall); Queen Square Battery (verbal and non-verbal recognition); Rey Auditory Verbal Learning Test
Jenkins et al., 1981	*Open-label* Repeated measures	5	-	-	264 (mid) (144 –384)	severe	**Desmopressin** – (DDAVP) Antidiuretic peptide	160Ug/day (4 daily intranasal dosages)	7 days	7.2	Progressive Matrices; Digit Span (forward & backward); Benton Visual Retention Test; Forced Choice Word Recognition; Cued Word Recall
PEPTIDE TREATMENTS											
POST-ACUTE											
Alvarez et al., 2008	*Open-label* Repeated measures	20	31.6 (2.24)	-	92	mild/ moderate/ severe	**Cerebrolysin** Neurotrophic peptide	30ml/day	5 days per week for 4 weeks (20 days)	8.3	Syndrome Kurztest
MIXED											
Alvarez et al., 2003	*Open-label* Repeated measures	20	30.1 (2)	-	81 (mid) (3 – 158)	mild/ moderate/ severe	**Cerebrolysin** Neurotrophic peptide	30ml/day	5 days per week for 4 weeks (20 days)	6.7	Glasgow Outcome Scale; Syndrome Kurztest

Cont'd

Table 5.B Cont'd

STUDY REFERENCE	STUDY DESIGN	TREATMENT GROUP N	TREATMENT GROUP AGE M(SD)	CONTROL GROUP AGE M(SD)	TIME TO TREATMENT (weeks)	SEVERITY	DRUG (Category)	DRUG DOSE	TREATMENT DURATION	QUALITY RATING	COGNITIVE/BEHAVIOURAL TESTS
PHOSPHOLIPID INTERMEDIATE											
POST-ACUTE											
Leon-Carrion et al., 2000	*RCT (blinding not reported)* Independent groups repeated measures	5	-	-	180 (min) (> 24)	severe	**Citicholine** (CDP choline) Superoxide radical scavenger	1g/day (via oral)	3 months (90 days)	4.8	Trail Making Test B; Sevillas Computerized Neuropsychological Test Battery; Verbal Fluency Task; Benton Visual Retention Test; Lurias Memory Words

Note: SSRI = Selective serotonin reuptake inhibitor; SNRI = Seratonin Noradrenaline reuptake inhibitor; RCT = randomised controlled trial.

Table 5.C: Chemical group, pharmacological category and method of action of drugs.

Chemical Group	Pharmacological Category	Method of Action	Drug (Brand Name)
Serotonergic	Antidepressant	SSRI	Sertraline (Zoloft) Citalopram (Ciprimil)
		Tricyclic	Amitriptyline (Tryptanol) Desipramine (Norpramin)
		SNRI	Milnacipran (Ixel)
		MAOI (Serotonin, Dopamine, Norepinephrine Agonist)	Phenelzine (Nardil)
Catecholamines	CNS Stimulant	Dopamine & Noradrenaline Release	Methylphenidate (Ritalin) Amantadine (Symmetrel)
	Anti-Parkinsonian Antipsychotic	Dopamine Release	Apomorphine (Apokyn)
		Dopamine Agonist	Quetiapine (Seroquel)
		Dopamine Antagonist	Ziprasidone (Geodon)
Cholinergic	Anti-dementia	Acetylcholinesterase inhibitor	Donepezil (Aricept) Physostigmine (Eserine)
		Acetycholine precursor	Lecithin
Sodium Channel Blocker	Antipsychotic/ Antiepileptic	Modulator of ion homeostasis	Carbamazepine (Tegretol)
Peptide	Anti-diuretic	Peptide	Lysine Vasopressin (LVP) Desmopressin (DDAVP/Stimate)
	Neurotrophic	Peptide	Cerebrolysin
Phospholipid Intermediate	Antioxidant	Inhibitor of free radical production	CDP-Choline (Citicholine)

Note: PEG-SOD = polyethyleglycol-conjugated superoxide dismutase; NMDA = n-methyl-D-aspartate; MAOI = monoamine oxidase inhibitor; SSRI = Selective serotonin reuptake inhibitor; SNRI = Serotonin noradrenaline reuptake inhibitor; CNS = Central Nervous System Stimulant

Appendix 5.A : Methodological quality rating system

	Question	Score
1	Demographically matched control group or condition provided	1
2	The control group is matched to the treatment group on initial performance	1
3	Patients were randomly allocated to groups	1
4	The method of randomization was provided	1
5	The cognitive or behavioural test is clearly described (or a reference provided)	1
6	The scores for each measure are specified (i.e. error, accuracy, speed)	1
7	The age of the participants is specified (M/SD/Range)	1
8	The severity of injury is specified	1
9	The measure/s of injury severity are provided (i.e. GCS, PTA, LOC)	1
10	The gender of participants is specified	1
11	Relevant premorbid demographic statistics are reported (e.g., education, IQ)	1
12	The initial sample size for each group is specified	1
13	The time from injury to treatment is specified	1
14	The drug dosage is specified	1
15	Significant test statistics are provided that would enable the calculation of an effect size (Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value)	1
16	The N for each group on each testing occasion is reported	1
17	Non-significant test statistics are reported that would enable the calculation of an effect size (Mean/Standard Deviation; t-score; F-ratio (one-way ANOVA) or exact p value)	1
18	Group allocation is blinded to the assessor	1
19	Group allocation is blinded to the patient	1
20	N lost to follow-up is reported	1
	TOTAL SCORE / 20	

Note: M = Mean score; SD = Standard deviation of score; GCS = Glasgow Coma Scale; PTA = duration of post-traumatic amnesia; LOC = duration of loss of consciousness; N = number of participants; IQ = intelligence quotient.

Table 5.D : Serotonergic treatments : Weighted effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
POST-ACUTE (> 4 weeks post-injury)									
DESIPRAMINE (Norpramin)									
Independent Groups Repeated Measures									
Affect/Mood Scale	Depression	1	10	24 – 120	severe	.36	1	73	Wroblewski et al., 1996[a]
AMITRIPTYLINE (Tryptanol)									
Repeated Measures									
HAM-D	Depression	2	23	32 – 39	mild	1.00*	9	45	Saran, 1988; Dinan & Moyayed, 1992[b]
CITALOPRAM (Ciprimil) & CARBAMAZEPINE (Tegretol)									
Repeated Measures									
Clinical Impression Scale	Psychosocial	1	20	84	severe	.91	4	48	Perino et al., 2001
Brief Psychiatric Scale	Psychosocial	1	20	84	severe	.60	2	62	Perino et al., 2001
PHENELZINE (Nardil)									
Repeated Measures									
HAM-D	Depression	1	10	32	mild	.55	2	62	Saran, 1988
MIXED (< 4 weeks - > 4 weeks post-injury)									
SERTRALINE (Zoloft)									
Independent Groups Repeated Measures									
Post Concussion Symptoms	Psychosocial	1	20	4	mild/moderate	-.86	3	48	Lee et al., 2005 (Study 2)
Motor Speed – CRT	Psychomotor Speed	1	20	4	mild/moderate	-.81	3	53	Lee et al., 2005 (Study 2)
Mental Arithmetic Test	General Cognition	1	20	4	mild/moderate	-.69	3	57	Lee et al., 2005 (Study 2)

Cont'd

Table 5.D Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
Choice Reaction Time	Cognitive Speed	1	20	4	mild/moderate	-.66	2	57	Lee et al., 2005 (Study 2)
WAIS Digit Symbol	Attention	1	20	4	mild/moderate	.65	2	57	Lee et al., 2005 (Study 2)
HAM-D	Depression	1	20	4	mild/moderate	.50	2	67	Lee et al., 2005 (Study 2)
Memory Scanning Task	Memory	1	20	4	mild/moderate	-.50	2	67	Lee et al., 2005 (Study 2)
Flicker Fusion Threshold	Arousal	1	20	4	mild/moderate	-.41	1	73	Lee et al., 2005 (St.udy 2)
BDI	Depression	1	20	4	mild/moderate	-.30	1	79	Lee et al., 2005 (Study 2)
Mini-Mental State Exam	General Cognition	1	20	4	mild/moderate	-.03	1	100	Lee et al., 2005 (Study 2)
Quality of Life Scales	Psychosocial	1	20	4	mild/moderate	.07	1	92	Lee et al., 2005 (Study 2)
Compensatory Tracking	Attention	1	20	4	mild/moderate	.10	1	92	Lee et al., 2005 (Study 2)
MILNACIPRAN (Ixel)									
Repeated Measures									
HAM-D	Depression	1	10	22	mild/moderate	1.85	7	21	Kanetani et al., 2003
Mini-Mental State Exam	General Cognition	1	10	22	mild/moderate	1.20	5	38	Kanetani et al., 2003

Note. $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to weighted effect size; Severity = range of injury severities contributing to combined effect size; M d_{wss} = mean effect size weighted by sample size; Nfs = Fail Safe N; OL% = percent overlap; HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; CRT = Choice Reaction Time.

* HAM-D : SD = .04, Min = .97, Max = 1.03.

Participants concurrently taking:

[a] psychoactive medications

[b] temazepam for night sedation

Table 5.E : Catecholamine treatments: Weighted effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
POST-ACUTE (> 4 weeks post-injury)									
METHYLPHENIDATE (Ritalin)									
Independent Groups Repeated Measures									
KAS – General Psychopathology	Psychosocial	1	38	116	severe	1.02	4	45	Mooney & Haas, 1993
State Trait Anger Scale	Anger/Aggression	1	38	116	severe	.83	3	53	Mooney & Haas, 1993
KAS - Belligerence	Anger/Aggression	1	38	116	severe	.82	3	53	Mooney & Haas, 1993
Profile of Mood States	Anger/Aggression	1	38	116	severe	.75	3	53	Mooney & Haas, 1993
Organic Signs & Symptoms	Psychosocial	1	38	116	severe	.75	3	53	Mooney & Haas, 1993
Working Memory Task	Memory	1	18	142	not specified	.51	2	67	Kim et al., 2006
Modified Posner Paradigm	Attention	1	18	142	not specified	.12	0	92	Kim et al., 2006
Cross-Over									
Distraction Task	Attention	1	19	74	mild/moderate/severe	.56	2	62	Whyte et al., 1997[1c]
Behavioural Inattention	Attention	1	19	74	mild/moderate/severe	.17	0	85	Whyte et al., 1997[1c]
Serial Digit Learning	Memory	1	12	208	moderate/severe	.14	0	92	Speech et al., 1993
GDS – Distractability	Attention	1	12	208	moderate/severe	.14	0	92	Speech et al., 1993
Choice Reaction Time	Cognitive Speed	2	31	74 – 208	mild/moderate/severe	.11*	0	92	Speech et al., 1993,Whyte et al., 1997[1c]
Phasic Arousal Task	Attention	1	19	74	mild/moderate/severe	.09	1	92	Whyte et al., 1997[1c]
Stroop Interference	Attention	1	12	208	moderate/severe	-.07	1	92	Speech et al., 1993
WAIS-R Digit Symbol	Attention	1	12	208	moderate/severe	.05	1	92	Speech et al., 1993
Memory Scanning Task	Memory	1	12	208	moderate/severe	-.05	1	92	Speech et al., 1993

Cont'd

Table 5.E Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
WAIS-R Digit Span	Attention	1	12	208	moderate/severe	.04	1	100	Speech et al., 199334
Selective Reminding Test	Memory	1	12	208	moderate/severe	.02	1	100	Speech et al., 199334
GDS – Vigilance	Attention	1	12	208	moderate/severe	.02	1	100	Speech et al., 199334
Visual Go/No-Go Task	Attention	1	19	74	mild/moderate/severe	.02	1	100	Whyte et al., 1997[1c]
APOMORPHINE (Apokyn)									
Repeated Measures									
Disability Rating Scale	Global outcome	1	7	10	severe	5.67	27	2	Fridman et al., 2010[d]
Coma Near-Coma Scale	Arousal	1	7	10	severe	4.44	21	2	Fridman et al., 2010[d]
AMANTADINE (Symmetrel)									
Repeated Measures									
COWAT	Verbal/Language	1	22	270	mild/moderate/severe	.31	1	79	Kraus et al., 2005
Complex Figure Test	Memory	1	22	270	mild/moderate/severe	.21	0	85	Kraus et al., 2005
Trail Making Test B	Attention	1	22	270	mild/moderate/severe	.17	0	85	Kraus et al., 2005
Trail Making Test A	Attention	1	22	270	mild/moderate/severe	.14	0	92	Kraus et al., 2005
CVLT	Memory	1	22	270	mild/moderate/severe	.14	0	92	Kraus et al., 2005
WAIS-R Digit Span	Attention	1	22	270	mild/moderate/severe	-.04	1	100	Kraus et al., 2005
QUETIAPINE (Seroquel)									
Repeated Measures									
Overt Aggression Scale-M	Anger/Aggression	1	7	99	mild/moderate/severe	4.25	20	4	Kim & Bijlani, 2006
Clinical Impression Scale	Psychosocial	1	7	99	mild/moderate/severe	4.25	20	4	Kim & Bijlani, 2006
NFI-Aggression	Anger/Aggression	1	7	99	mild/moderate/severe	2.00	9	19	Kim & Bijlani, 2006

Cont'd

Table 5.E Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
RBANS	Memory/Attention	1	7	99	mild/moderate/severe	2.00	9	19	Kim & Bijlani, 2006
ZIPRASIDONE (Geodon)									
Repeated Measures									
Agitated Behaviour Scale	Anger/Aggression	1	5	8	severe	3.07	14	7	Noe et al., 2007
MIXED (< 4 weeks - > 4 weeks post-injury)									
METHYLPHENIDATE (Ritalin)									
Independent Groups Repeated Measures									
HAM-D	Depression	1	20	4	mild/moderate	1.59	7	27	Lee et al., 2005 (Study 1)
Post Concussion Symptoms	Psychosocial	1	20	4	mild/moderate	.67	2	57	Lee et al., 2005 (Study 1)
Quality of Life Scales	Psychosocial	1	20	4	mild/moderate	.61	2	62	Lee et al., 2005 (Study 1)
BDI	Depression	1	20	4	mild/moderate	-.51	2	67	Lee et al., 2005 (Study 1)
WAIS Digit Symbol	Attention	1	20	4	mild/moderate	.46	1	67	Lee et al., 2005 (Study 1)
Mini-Mental State Exam	General Cognition	1	20	4	mild/moderate	.26	0	79	Lee et al., 2005 (Study 1)
Compensatory Tracking	Attention	1	20	4	mild/moderate	.23	0	85	Lee et al., 2005 (Study 1)
Memory Scanning Task	Memory	1	20	4	mild/moderate	.08	1	92	Lee et al., 2005 (Study 1)
Motor Speed – CRT	Psychomotor Speed	1	20	4	mild/moderate	-.07	1	92	Lee et al., 2005 (Study 1)
Flicker Fusion Threshold	Arousal	1	20	4	mild/moderate	-.05	1	92	Lee et al., 2005 (Study 1)
Mental Arithmetic Test	General Cognition	1	20	4	mild/moderate	.04	1	100	Lee et al., 2005 (Study 1)
Choice Reaction Time	Cognitive Speed	1	20	4	mild/moderate	.04	1	100	Lee et al., 2005 (Study 1)

Cont'd

Table 5.E Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
Cross-Over									
SustainedAttention to Response	Attention	1	40	8	moderate/severe	.10	1	92	Willmott & Ponsford, 2009
Attentional Behaviour	Attention	1	40	8	moderate/severe	.10	1	92	Willmott & Ponsford, 2009
Four Choice Reaction Time	Attention	1	40	8	moderate/severe	.05	1	92	Willmott & Ponsford, 2009
Symbol Digit Modalities	Attention	1	40	8	moderate/severe	-.03	1	100	Willmott & Ponsford, 2009
Ruff 2 & 7 Test	Attention	1	40	8	moderate/severe	-.02	1	100	Willmott & Ponsford, 2009
Letter Number Sequencing	Attention	1	40	8	moderate/severe	.01	1	100	Willmott & Ponsford, 2009
Selective Attention Task	Attention	1	40	8	moderate/severe	-.01	1	100	Willmott & Ponsford, 2009
AMANTADINE (Symmetrel)									
Independent Groups Repeated Measures									
Disability Rating Scale	Global Outcome	1	35	4	moderate/severe	.83	3	53	Meythaler et al., 2002
GOS (6 weeks)	Global Outcome	1	35	4	moderate/severe	.80	3	53	Meythaler et al., 2002
Mini-Mental State Exam	General Cognition	1	35	4	moderate/severe	.31	1	79	Meythaler et al., 2002
Functional Independence	Psychosocial	1	35	4	moderate/severe	-.30	1	79	Meythaler et al., 2002

Note: $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to weighted effect size; Severity = range of injury severities contributing to combined effect size; M d_{wss} = mean effect size weighted by sample size; Nfs = Fail Safe N; OL% = percent overlap; Nfs = Fail Safe N; OL% = percent overlap; GDS = Gordon Diagnostic System; GOS = Glasgow Outcome Scale; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; NFI = Neurobehavioural Functioning Inventory; HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

[1] Single group repeated cross-over design

* Choice Reaction Time : SD = .06, Min = .06, Max = .15

Participants concurrently taking

[c] carbemazepine

[d] anti-epileptic and anti-spasticity drugs

Table 5.F : Cholinergic treatments: Weighted effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
POST-ACUTE (> 4 weeks post-injury)									
DONEPEZIL (Aricept)									
Independent groups repeated measures									
Paced Auditory Serial Addition Test	Attention	1	18	18	mild/moderate/severe	2.93	14	7	Zhang et al., 2004
Weschler Memory Scale-(original/III)	Memory	2	44	18 - 21	mild/moderate/severe	1.56*	15	27	Zhang et al., 2004; Kim et al., 2009
Boston Naming Test	Memory	1	26	21	not specified	1.56	7	27	Kim et al., 2009
Mini Mental State Exam	General Cognition	1	26	21	not specified	1.27	5	35	Kim et al., 2009
Coloured Progressive Matrices	General Cognition	1	26	21	not specified	.31	1	79	Kim et al., 2009
Repeated measures									
Rey Auditory Verbal Learning Test	Memory	1	4	174	severe	1.59	7	27	Masanic et al., 2001
Complex Figure Test	Memory/Perception	1	4	174	severe	.85	3	48	Masanic et al., 2001
Rivermead Memory Test	Memory	1	4	174	severe	.61	2	62	Masanic et al., 2001
Memory Assessment Scale	Memory	1	10	63	mild/moderate/severe	-.56	2	62	Kaye et al., 2003
Rey Auditory Verbal Memory Test	Memory	1	10	180	moderate/severe	.53	2	67	Khateb et al., 2005
Reaction Time – Dual Task	Attention	1	10	180	moderate/severe	.50	2	67	Khateb et al., 2005
Dysexecutive Questionnaire	Psychosocial	1	10	180	moderate/severe	.47	1	67	Khateb et al., 2005
Stroop Colour	Attention	1	10	180	moderate/severe	.34	1	79	Khateb et al., 2005
Non-verbal Fluency (figural/categorical)	Executive	1	10	180	moderate/severe	.26	0	79	Khateb et al., 2005
Visual Span	Attention	1	10	180	moderate/severe	.25	0	79	Khateb et al., 2005
Trail Making Test B	Attention	1	10	180	moderate/severe	.25	0	79	Khateb et al., 2005

Cont'd

Table 5.F Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
Hospital Anxiety & Depression Scale	Depression	1	10	180	moderate/severe	.23	0	85	Khateb et al., 2005
Stroop Interference	Attention	1	10	180	moderate/severe	.22	0	85	Khateb et al., 2005
Verbal span	Attention	1	10	180	moderate/severe	.20	0	85	Khateb et al., 2005
Trail Making Test A	Attention	1	10	180	moderate/severe	.17	0	85	Khateb et al., 2005
Verbal Fluency	Verbal /Language	1	10	180	moderate/severe	.09	1	92	Khateb et al., 2005
Stroop Word	Attention	1	10	180	moderate/severe	.09	1	92	Khateb et al., 2005
PHYSOSTIGMINE (Eserine) + LECITHIN									
Independent groups repeated measures									
Continuous Performance Test	Attention	1	16	20	moderate/severe	.30	1	79	Levin et al., 1986
Digit Cancellation	Attention/Perception	1	16	20	moderate/severe	-.29	1	79	Levin et al., 1986
Selective Reminding Test	Memory	1	16	20	moderate/severe	-.16	0	85	Levin et al., 1986
Visual Recognition Memory	Memory	1	16	20	moderate/severe	-.05	1	92	Levin et al., 1986
Digit Span	Attention	1	16	20	moderate/severe	.01	1	100	Levin et al., 1986
MIXED (< 4 weeks - > 4 weeks post-injury)									
DONEPEZIL (Aricept)									
Independent groups									
Functional Independence Measure	Psychosocial	1	28	5	moderate/severe	.18	0	85	Walker et al., 2004

Note: $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to effect size; Severity = range of injury severities contributing to effect size; M d_{wss} = mean effect size weighted by sample size; Nfs = Fail Safe N; OL% = percent overlap.

* SD = 1.53, Min = .67, Max = 2.84

Table 5.G : Sodium Channel Blockers (modulators of ion homeostasis) : Weighted effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{particpants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
POST-ACUTE (> 4 weeks post-injury)									
CARBAMAZEPINE (Tegretol)									
Repeated Measures									
Shortened Neurobehavioural	Psychosocial	1	10	58	severe	2.20	10	16	Azouvi et al., 1999[e]
Global Neurobehavioural	Psychosocial	1	10	58	severe	1.90	9	21	Azouvi et al., 1999[e]
Agitated Behaviour Scale	Anger/Aggression	1	10	58	severe	1.01	4	45	Azouvi et al., 1999[e]
Mini-Mental State Exam	General Cognition	1	10	58	severe	.12	0	92	Azouvi et al., 1999[e]

Note. . $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to weighted effect size; Severity = range of injury severities contributing to combined effect size; M d_{wss} = mean effect size weighted by sample size; Nfs = Fail Safe N; OL% = percent overlap.

Participants concurrently taking:

[e] neuroleptics

Table 5.H : Peptide treatments: Weighted effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
POST-ACUTE (> 4 weeks post-injury)									
LYSINE VASOPRESSIN (LVP)									
Repeated measures									
Weschler Memory Scale	Memory	1	26	256	severe	.62	2	62	Eames & Wood, 1999
Rey Auditory Verbal Learning Test	Memory	1	26	256	severe	.43	1	73	Eames & Wood, 1999
Queen Square Battery	Memory	1	26	256	severe	.33	1	79	Eames & Wood, 1999
CEREBROLYSIN									
Repeated measures									
Syndrome Kurztest	Memory/Attention	1	20	92	mild/moderate/severe	.41	1	73	Alvarez et al., 2008
DESMOPRESSIN (DDAVP)									
Repeated measures									
Word Recognition	Memory	1	5	391	severe	-.39	1	73	Jenkins et al., 1981
Word Recall	Memory	1	5	391	severe	-.38	1	73	Jenkins et al., 1981
Benton Visual Retention Test	Memory	1	5	391	severe	.29	1	79	Jenkins et al., 1981
Digit Span	Attention	1	5	391	severe	-.16	0	85	Jenkins et al., 1981
Progressive Matrices	General Cognition	1	5	391	severe	.07	1	92	Jenkins et al., 1981

Cont'd

Table 5.H Cont'd

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{participants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
MIXED (< 4 weeks - > 4 weeks post-injury)									
CEREBROLYSIN									
Repeated measures									
Syndrome Kurztest	Memory/Attention	1	20	81	mild/moderate/severe	1.54	7	29	Alvarez et al., 2003[g]
GOS (1 month)	Global Outcome	1	20	81	mild/moderate/severe	.83	3	53	Alvarez et al., 2003[g]

Note: $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to effect size; Severity = range of injury severities contributing to effect size; M d_{wss} = mean effect size weighted by sample size; Nfs = Fail Safe N; OL% = percent overlap; GOS = Glasgow Outcome Scale.

Participants concurrently taking:

[f] citicholine and piracetam

[g] Participants concurrently taking anticonvulsants

Table 5.I : Phospholipid Intermediates : Weighted effect sizes for cognitive and behavioural measures.

Drug and Measure	Psychological Construct	$N_{studies}$	$N_{particpants}$	Injury to Treatment (weeks)	Injury Severity	M d_{wss}	Nfs	OL%	Study Reference
POST-ACUTE (> 4 weeks post-injury)									
CDP-CHOLINE (Citicholine)									
Independent Groups Repeated Measures									
Visual Retention Test	Memory	1	10	180	severe	.62	2	62	Leon-Carrion et al., 2000
Lurias Memory Words	Memory	1	10	180	severe	.51	2	67	Leon-Carrion et al., 2000
Neuropsychological Battery	Attention	1	10	180	severe	-.45	1	67	Leon-Carrion et al., 2000
Verbal Fluency	Verbal/Language	1	10	180	severe	.36	1	73	Leon-Carrion et al., 2000
Trail Making Test B	Attention	1	10	180	severe	-.09	1	92	Leon-Carrion et al., 2000

Note: $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants contributing to weighted effect size; Severity = range of injury severities contributing to combined effect size; M d_{wss} = mean effect size weighted by sample size; Nfs = Fail Safe N; OL% = percent overlap; Nfs = Fail Safe N; OL% = percent overlap.

Chapter 6

Appendix 6.A: Summary of treatments that showed efficacy in $N_{Treatment\ Studies} \geq 1$

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
Serotonergic			
8-OH-DPAT	.80		
Amitriptyline			1.00
Citalopram + Carbemazepine			.60 - .91[1]
Phenelzine			.55
Sertraline			-.86 - .65[1]
Milnacipran			1.20 – 1.85[1]
BAY X3702		-	
Desipramine			-
Catecholamines			
Rasagline	2.02		
Haloperidol	-1.49		
Methylphenidate	1.48		-.51 – 1.59[1]
L-Deprenyl	1.01		
Apomorphine	-		4.44 – 5.67[1]
Ziprasidone			3.07
Quetiapine			2.00 – 4.25[1]
Amantadine		1.86	.80 - .83[1]
Risperidone	-		
Sulpiride	-		
Rasagline + Scopolamine	-		
Sulpiride + SCH 23390	-		
SCH 23390	-		
Cholinergic			
LU 25-109-T	1.27		
ENA 713 + Scopolamine	-1.23		
ENA 713	.88 – 2.40[1]		
Scopolamine	.82		
ENA 713 + Mecamylamine	-		
THA	-		
Mecamylamine	-		

Cont'd

Appendix 6.A Cont'd

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
Physostigmine + Lecithin			-
Donepezil			-.56 – 2.93[1]
Modulators of Ion Homeostasis			
Calcium			
SNX - 185	.85 – 2.17[1]		
Ziconotide	1.17 – 1.70[1]		
S100B	-		
BMS-204352	-		
Nimodipine		-	
Sodium			
Carbemazepine			1.01 2.20[1]
Thyrotropin-Releasing Hormone Analogues			
TRH 35b	5.70		
YM 14673	1.43		
YM 14673 + Nalmefene	1.33		
2-ARA-53a	.93		
Vasodilators			
SB 209670	1.94		
SB 234551	1.56		
Opioids			
Nalmefene + Dextrorphan	1.25		
Nalmefene	-		
Nor-BNI	-		
Morphine	-		
Anti-inflammatories			
B3	.91 – 4.09[1]		
VCP	2.37 – 3.56[1]		
Simvastatin	2.49		
Atorvastatin	1.41 – 2.43[1]		
C1-INH	.90 – 1.30[1]		

Cont'd

Appendix 6.A Cont'd

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
Minocycline HCl	1.03		
IL-18BP	1.00		
COG 1410	.95		
IL-10	-		
CP-0127		6.07	
LF-16-0687Ms		-	
Antidiuretics			
V-1880	-		
V-2381	-		
Immunosuppressants			
Cyclosporin A	3.02		
Rapamycin	-		
Modulators of Free Radical Formation			
Bemithyl	1.00 – 16.49[1]		
DETA/NONOate	2.53 – 3.40[1]		
CDP-Choline	.97 – 1.76[1]		.51 - .62[1]
PBN	1.66		
B2	1.14 – 1.60[1]		
DMSO	1.27		
Murine IgG	1.23		
Anti-ICAM	1.19		
L-NIL	1.19		
Inosine	1.15		
1400W	.98		
AG	-		
7-NI	-		
S-PBN	-		
L-NAME	-		
Pen ME	-		
Melatonin	-		
PEG-SOD		-	

Cont'd

Appendix 6.A Cont'd

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
Steroids			
Raloxifene	1.14		
Progesterone	-		
Methylprednisolone		-	
Modulators of Amino Acid Activity			
MgCl + B2	15.64		
MgSO	1.14 – 1.81[1]		
CP-98,113	.94 – 1.66[1]		
HU-211 (Dexanabinol)	1.53 – 1.60[1]	-	
MgCl	1.03 – 1.43[1]		
½MgCl + ½B2	1.24		
Dextrorphan	1.20		
CP-101,606	1.07	-	
CP-101,581	1.04		
DCS	.87 – 1.03[1]		
Aniracetam	.91		
Eliprodil	.88		
MDL 26,479	-		
Ketamine	-		
NPS 1506	-		
GK-11		-	
Growth Factors			
EPO + BrdU	2.38		
EPO	.97 – 1.41[1]		
NGF	1.07		
mAB 7B12	-		
Other			
Pyracetam	1.07 – 8.41[1]		
FDP + DMSO	4.78		
NIM 811	3.85		
FTS	.88 – 2.28[1]		

Cont'd

Appendix 6.A Cont'd

CATEGORY AND DRUG	**Study 1** : Rodent Acute ($d \geq .8$)	**Study 2** : Human Acute ($d \geq .5$)	**Study 3** : Human Post-acute ($d \geq .5$)
GTSs	-1.91		
Fenofibrate	1.50		
HSA	1.47		
sAPPa	-1.02		
INO-1001	.93		
FDP	.86		
2-AG	-		
Lactate	-		
Nizofenone	-		
Levetiracetam	-		
OKY-046	-		
VA-045	-		
NBP	-		
Desmopressin		-	-
Lysine Vasopressin			.62
Cerebrolysin			.83 – 1.54[1]
Total Treatments	91	11	19

Note: - = treatment examined but not efficacious in this group

[1] Indicates the range of large (rodent) or moderate (human) effect sizes for different outcome measures

APPENDIX 7.A:

Wheaton, P., Mathias, J.L. & Vink, R. (2009) Impact of Early Pharmacological Treatment on Cognitive and Behavioral Outcome After Traumatic Brain Injury in Adults: A Meta-Analysis *Journal of Clinical Psychopharmacology, v. 29 (5), pp. 468-477*