

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 (American 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

R. Vink

Date

List of Abbreviations

AMPA	α -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	γ -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