Traumatic Brain Injury in Children — A Review of Pharmacological Approaches to Acquired ADHD

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BACKGROUND

- Traumatic brain injury (TBI), a common condition seen in both adults and children, can lead to cognitive, social and physical complications.
- Attention Deficit/Hyperactivity Disorder (ADHD) induced by TBI (secondary ADHD or ADHD/TBI) in children is one consequence that has limited discussion in the literature.

OBJECTIVE

This poster reviews the psychopharmacologic treatment options available, their effectiveness, and what is currently under study.

METHODS

- A literature search was conducted using the following databases: Medline, Cochrane/EBM and PubMed from 1988-2011.
- Stimulants TBI, TBI, ADHD TBI, Bromocriptine, Guanfacine, Donepazil and Atomoxetine were the key search terms used.
- Limits include clinical trial publication, human subjects, English language, adults and children age 0-18 years.
- Information was extracted on study characteristics, interventions and outcome.
- Data extracted included subjective and objective tests use to measure behavioral and cognitive outcomes. *(see details in Tables)*

RESULTS

- Eleven clinical trials evaluating the efficacy and safety of Methylphenidate (MPH) in pediatric and adult patients with TBI match the search criteria. *(see details in Table 1)*
- Methylphenidate administration resulted in a statistically significant increase in pulse of 12.3 beats/min (95% confidence interval (CI) 9.25–15.36), diastolic blood pressure of 4.1 mmHg (95% CI 2.11–6.10), and mean arterial pressure of 3.75 mmHg (95% CI 1.79–5.72). These changes did not, however, appear to be symptomatic, as no participants were withdrawn due to adverse events, and there was no significant self-report of increased heart rate with methylphenidate. (Catherine Willmott et. al 2009)

Table 1: Published Clinical Studies for Methylphenidate in TBI

Reference	Design	Pts. (N)	GCS Score[1]	Start of Treatment Post Injury	Trial Length (days)	Dosage (mg/kg BID)	Outcomes Measures	Results
Gualtieri et al. (1998)	R, DB, PC, crossover	15	<8	5 mo-12 y	12	0.15-0.30	Attention, memory	Some symptomatic improvement in memory
Mooney et al. (1993)	R, PC, single-blind	38	<8	>=6 mo	42	4 wks titration 30 mg/day at wk 5 & 6	Anger, memory, attention psychological and social adjustment, adverse effects	Effective in anger, memory improvement
Speech et al. (1993)	R, DB, PC	12	NR	14 mo-9 y	7	0.3	Attention, learning, cognitive processing speed, social behavior	No significant difference in methylphenidate vs placebo
Williams et al. (1998)	DB, PC, crossover	10	NR	2 mo – 9y	4	0.25 – 0.35	Attention, memory, behavior, processing speed, psychomotor speed	No significant difference in any outcomes with methylphenidate vs placebo
Mahalick et al. (1998)	R, DB, PC, crossover	14	3-15	1 mo- 5 y	14	0.3	Attention disorders	Significant improvement in all tasks of attention and concentration with methylphenidate vs placebo
Kaelin et al. (1996)	Prospective, multiple baseline (A-A-B-A)	10	3-13	4 days – 2 mo			Attention, functional outcome	Significant improvement in attention with methylphenidate vs natural recovery
Whyte et al.(1997)	R, DB, PC, crossover	19	3-14	1 mo – 8 y	N/A	0.25	Attention	Significant improvement in mental processing speed
Whyte et al. (2004)	R, DB, PC, crossover	34	<12	>= 3 mo			Attention	Improvement in the speed of processing information, some aspects of on-tasks behavior improved with methylphenidate
Plenger et al. (1996)	R, DB, PC, crossover	23	4-13[2]	NR			Attention, memory, vigilance	Attention and motor function improved with methylphenidate at 30 day evaluation
Alban et al. (2004)	R, DB, PC, crossover	35	<12	4 mo-34 y			Adverse effects, vital signs	Poor appetite, mean rise in arterial pressure 2.5 mm Hg, pulse increased by 7 beats/min
Hornyak et al. (1996)	Chart review	10	<8		Set by individual clinician, detail N/A	Set by individual clinicians, detail not available	Attention	Improvement in attention, impulsivity, level of activity, agitation, responsivity and arousal

DB = double-blind; GCS = Glasgow Coma Scale; NR = not reported; PC = placebo-controlled; R = randomized; TBI = traumatic brain injury
[1] The following scores indicate the severity of TBI; severe 1-8; moderate 9-12; and mild 13-15
[2] Complicated, mild to moderately severe TBI

Table 2: Published Clinical Studies on Non-Stimulant Medication in Secondary ADHD

Reference	Medication	Design	Pts (N)	Duration of Treatment	Dose Used	Outcome Measures	Results
Zhang et al. (2004)	Donepazil	R, DB, PC, Crossover	18	24 wks	5-10 mg daily	Short term memory, sustain attention	Donepazil increased neuropsychologic testing scores in short- term memory and sustained attention.
Whyte jet et al. (2008)	Bromocriptine	DB, PC, Crossover	12	6 wks	5 mg BID	Attention and work productivity	Bromocriptine in a dose of 5 mg BID does not seen to enhance attentional skills, and it may be associated with an excess of adverse events. It is not clear whether intermediate dosing or lower dose might confer benefit.
Thomas W. Mcallister et al. (2011)	Alpha adrenergic agent (Guanfacine)	PC, DB, Crossover	13	37 days	2 mg daily	Working memory (ability to hold info in mind) No info on attentional component	It is associated with increased working memory performance.
Wendy M Reid et al. (2008)	Atomoxetine	-	-	-	-	-	Improves cognition Following experimental TBI in animals. No study on human subjects.

RESULTS CONT.

- Methylphenidate was safely used in brain injured patients, even those at high risk for seizures, as it was associated with a trend toward reduction (rather than increase) in seizure frequency in this population. (Wroblewski et. al, 1992)
- (See results of published clinical studies on non-stimulant medications in secondary ADHD in Table 2.)
- Many drugs showed encouraging pre-clinical results with neuroprotective, neurorestorative, neurogenetic and synaptogenetic properties but all phase II and III clinical trials have failed so far. They include Progesterone, Dexabinol, Dexamethasone Magnesium, Cyclosporin A, Erythropoietin (and its carbamylated form), Statins, and Bone marrow stromal cells. (Robert Vink et. al '04), (Ye-Xione et. al '09)

CONCLUSION

- There are a limited number of randomized double blind placebo controlled multicenter trials studying the effects of methylphenidate in ADHD/TBI.
- No randomized controlled studies in ADHD/TBI using stimulants other than MPH were found.
- Statistical analyses of the limited data demonstrate the efficacy of short term treatment with MPH in the pediatric population.
- There is very scant literature available on the use of non stimulant treatment options in Secondary ADHD.

RECOMMENDATIONS

- More studies are required to see the effects of amphetamine group of stimulants and non-stimulant treatment options for secondary ADHD.
- Based on our review, additional multicenter, randomized, double blind, placebo controlled studies with larger sample sizes, longer length of treatment and wider dose ranges would be helpful in guiding clinical practice.