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Primary sources

Search terms
Search terms (designed for Medline and tailored accordingly for other sources) were: (exp Brain Injuries/OR Brain Neoplasms/ OR brain adj2 injur* OR head adj2 injur* OR brain adj2 tumor* OR neurooncolog* OR neuro-oncolog* OR brain adj2 cancer* OR brain adj2 neoplasm* OR brain adj2 carcinoma* OR head adj2 trauma* OR brain adj2 trauma* OR cerebrovascular adj2 trauma*) AND (exp “Attention Deficit and Disruptive Behavior Disorders”/ OR exp Attention Deficit Disorder with Hyperactivity/ OR exp Attention/ OR exp Hyperkinesis/ OR exp Impulse Control Disorders/ OR exp Impulsive Behavior/ OR attention* OR hyperactiv* OR impulsiv* OR ADHD* OR AD* OR HD* OR hyperkine* OR ADD* OR learn* OR cogniti* OR neuro- psychol* OR neuro-psychol* OR educat* OR attain* OR achieve* OR intell*) AND (exp Central Nervous System Stimulants/ OR stimulant* OR methylphenidate OR MPH OR atomoxetine OR methyl-amphetamine OR pemoline). For children with an acquired brain injury (ABI), 11-year-old boy is struck by a car and sustains an acquired brain injury (ABI). He is admitted with a Glasgow Coma Scale score of 6/15. Cranial imaging reveals evidence of diffuse injury. Approximately 12 months later following discharge, the patient is seen for a planned review. The patient and his family report poor attention with hyperactive and impulsive behaviours. The school has reported him as being disruptive in class. This represents a clear departure from the patient’s preinjury behaviour. Parental and school management of this concerning conduct is structured and consistent. You have heard that stimulant medication may be of benefit in managing difficulties with attention, hyperactivity and impulsivity (attention deficit hyperactivity disorder [ADHD] type behaviours) following an ABI.

Structured Clinical Question
For children with an acquired brain injury (patient), does the administration of stimulant medication [intervention] help address inattention, impulsivity and hyperactivity [outcomes]?

Search Strategy and Outcome
Secondary sources
The Cochrane Library (including Cochrane Reviews, Database of Abstracts of Review of Effects and Clinical Trials) was searched.

Commentary
The largest groups comprising paediatric ABI are traumatic brain injury (TBI) and brain tumours. During 2009–2010, TBI accounted for over 34,000 admissions to UK hospitals for patients under the age of 15 years, with malignant neoplasms of the eye, brain and central nervous system accounting for over 6500. These children are at an increased risk of deficits in attention, working memory and processing speed which may lead to the secondary consequences of IQ loss, academic failure and vocational and social problems. There is well established evidence for hyperactivity, memory impairment and inattention leading to diminished adaptive functioning and social judgement. Stimulants, in particular methylphenidate (MPH), have been used to treat deficits in attention and ADHD with demonstrated successes. While the published literature repeatedly indicates the need to consider pharmacological approaches to manage difficulties with attention and hyperactivity following paediatric ABI, this remains at odds with routine clinical practice. While ADHD type behaviours and their consequences may typically be regarded as more synonymous with TBI, it is important to note that these concerns are reported within the wider ABI population of children with brain tumours or acute lymphoblastic leukaemia (ALL).

The advanced systematic review retrieved 16 studies (table 3 and online supplementary table) examining the effectiveness of stimulants following paediatric ABI. All studies were conducted in the USA. The first published use of MPH for paediatric ABI occurred in 1986 with the first published use of stimulants for paediatric oncology in 1992. All papers described in table 3 use a placebo controlled, double blind, crossover trial with variants of randomised assignment. Forms of assignment are described variably or not at all and use of a washout period is consistent. Eight studies examined MPH use with mixed paediatric brain tumour patients and ALL samples. Eight retrieved papers evaluated MPH use after TBI. Five of these met level 2b evidence criteria. No studies solely examined use of MPH with brain tumours as participants with ALL were always included. In these studies, the neurooncology samples were heterogeneous with no clear delineation between tumour types and oncological interventions. These studies used a variety of doses, in very heterogeneous groups. There may be an influence of the type of treatment received, for example radiotherapy when very young and the type of brain tumour upon the outcome, and this is not fully explored here. Non-level 2b studies (online supplementary table) met level 5 criteria and used an AAB single case study design, case reviews or retrospective chart reviews. For all studies, the maximum reported MPH dosage ranged from 0.3 mg/kg twice daily to 36 mg daily, with a MPH treatment duration range from 1 day to only one paper demonstrating long term use at 6 years. One paper purposely fully assessed for the presence of adverse side effects and demonstrated that MPH was well tolerated with subgroup characteristics (female, lower IQ) being identified as predictive for an increased risk of adverse side effects.
### Table 3: Should stimulants be administered to manage difficulties with attention, hyperactivity and impulsivity following paediatric acquired brain injury?

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gualtieri et al</td>
<td>N=15 with TBI (aged 12–44, n&lt;19 years=6). Max dosage 0.3 mg/kg twice daily. Treatment period 12 days</td>
<td>RCT (level 2b)</td>
<td>Adult activity ques tonnaires, measures of memory and attention and family and patient interview</td>
<td>Ten responders with subjective and objective evidence of a 'positive' drug response. Significant MPH vs placebo effect.</td>
<td>Carry-over effects obscured drug effects. Administered adult psychometrics.</td>
</tr>
<tr>
<td>Clark et al</td>
<td>N=8 with TBI (aged 7–15). Max dosage 0.6 mg/kg twice daily. Treatment period 2 weeks</td>
<td>RCT (level 2b)</td>
<td>Two behvioral questionnaires and six psychometric tests of attention</td>
<td>Statistically significant MPH vs placebo effect on two psychometric tests and one behavioural measure. Results suggest that stimulant medication may be useful in improving attention.</td>
<td>One child diagnosed with ADHD preinjury. Injury 6–43 months prior to study and varied severity of injury.</td>
</tr>
<tr>
<td>Plenger et al</td>
<td>N=12 with TBI (aged 16–64, n&lt;19 years=unknown). Max dosage 0.3 mg/kg twice daily. Treatment period 30 days</td>
<td>RCT (level 2b)</td>
<td>Measures of memory, attention and functioning</td>
<td>Significant MPH vs placebo effect in functioning (p&lt;0.02), attention (p&lt;0.03) and motor performance (p&lt;0.05) at 30 days. No significant difference at 90 days.</td>
<td>Subacute administration of MPH after TBI enhanced rate but not ultimate level of recovery. Pilot randomised double-blind MPH–placebo cross-over trial.</td>
</tr>
<tr>
<td>Torres et al</td>
<td>N=6 with BT (aged 8–20 years). Max dosage 0.3 mg/kg twice daily. Treatment period 2 weeks</td>
<td>RCT (level 2b)</td>
<td>Behavioural measures of neurocognitive performance and teacher ratings</td>
<td>MPH at standard dose of 0.3 mg/kg twice daily did not have a significant effect on attention or memory.</td>
<td></td>
</tr>
<tr>
<td>Mahalick et al</td>
<td>N=14 (aged 5–14) with TBI. Max dosage 0.3 mg/kg twice daily. Treatment period 14 days</td>
<td>RCT (level 2b)</td>
<td>Measures of attention and concentration</td>
<td>Significant MPH vs placebo effect in improving all tasks of attention and concentration (p&lt;0.04)–(p&lt;0.005).</td>
<td></td>
</tr>
<tr>
<td>Williams</td>
<td>N=10 with TBI (aged 5–16). Max dosage 10 mg twice daily. Treatment period 4 days</td>
<td>RCT (level 2b)</td>
<td>Measures of hyperactivity, attention, memory, processing speed and psychomotor skills</td>
<td>No significant MPH vs placebo effect in any outcome measure.</td>
<td></td>
</tr>
<tr>
<td>Thompson et al</td>
<td>N=32 with ALL or BT (aged 6.4–7.15) and CT and/or RT. Max dosage 20 mg daily. Treatment period 1 day</td>
<td>RCT (level 2b)</td>
<td>Measures of attention and memory</td>
<td>Significant MPH vs placebo effect in errors of omission/sus. Baseline results higher than expected in children of tained attention (p&lt;0.015), overall index (p&lt;0.008) but not similar age in general population. Errors of commission/impulsiveness or reaction times.</td>
<td></td>
</tr>
<tr>
<td>Mulhem et al</td>
<td>N=83 with ALL or BT (aged 6.7–17.9). Max dosage 20 mg twice daily. Treatment period 5 days</td>
<td>RCT (level 2b)</td>
<td>Behavioural questionnaires of hyperactivity and social skills</td>
<td>Significant MPH vs placebo effect on attention and cognitive behaviour reported by parents and teachers (p&lt;0.001–p&lt;0.045). Teachers reported improvements in social behaviours and academic competence.</td>
<td>Sufficient power to detect an effect size of at least 0.30 at p&lt;0.05 (two-tailed). Three participants demonstrated serious adverse reactions and MPH was ceased.</td>
</tr>
<tr>
<td>Conklin et al</td>
<td>N=122 with ALL or BT (aged 6–18) and CT and/or RT. Max dosage 20 mg twice daily. Treatment period 1 day</td>
<td>RCT (level 2b)</td>
<td>Measures of memory, attention and academic achievement</td>
<td>Significant MPH vs placebo effect on a measure of attention, cognitive flexibility and processing speed (p=0.047).</td>
<td>Male gender, older age at treatment and higher IQ were predictive of better medication response. No significant differences were identified for number or severity of adverse side effects as a function of MPH. Floor effects and practice effects could be confounders.</td>
</tr>
<tr>
<td>Conklin et al</td>
<td>N=103 with ALL or BT (aged 6–18) and CT and/or RT. Max dosage 20 mg twice daily. Treatment period 5 days. Follow-up trial to Conklin et al</td>
<td>RCT (level 2b)</td>
<td>Carer rated side effect questionnaires</td>
<td>Significantly higher number and severity of symptoms with moderate dose compared with placebo or low dose (p&lt;0.001), but not low dose compared with placebo.</td>
<td>Female gender and lower IQ associated with greater adverse effects. Severity of side effects at baseline was greater compared with low dose but not moderate dose. Logistic regression examined predictors of “+” response. Demographic or clinical variables, intensity of central nervous system treatments, or time since treatment of global cognitive measures were not predictive of MPH response. Parental and teaching screening ratings were predictive.</td>
</tr>
<tr>
<td>Conklin et al</td>
<td>N=106 with ALL or BT (aged 7–18). Max dosage 20 mg twice daily. Treatment period 5 days. Follow-up trial to Conklin et al</td>
<td>RCT (level 2b)</td>
<td>Behavioural questionnaires of hyperactivity and social skills</td>
<td>45.28% showed decrease in teacher rated attention problems (p&lt;0.05).</td>
<td></td>
</tr>
<tr>
<td>Conklin et al</td>
<td>N=68 with ALL or BT (aged 6–18). Max dosage 36 mg daily. Treatment period 12 months. Follow-up trial to Conklin et al</td>
<td>RCT (level 2b)</td>
<td>Measures (direct and proxy) of attention and academic attainment</td>
<td>Attention and behavioural benefits of MPH demonstrated and maintained across settings. Academic gains were not demonstrated.</td>
<td>A greater period of follow-up may be required for academic gains to be realised.</td>
</tr>
</tbody>
</table>
The retrieved papers chart progressive changes to the methodology used to investigate the effectiveness of MPH for paediatric ABI with a trend of strengthened study design and increased dosage and treatment duration. Different multiple measures, both direct and proxy, are utilised and selected screening tools also serve as outcome measures. Screening tools may be insufficiently sensitive to determine the presence of change and consensus further for what constitutes outcome is absent. The majority of studies evaluate the presence of change using neurocognitive assay. No retrieved study provides a clearly stated developmental neurocognitive model to guide clinical reasoning and intervention. The principal limitations of the retrieved evidence base for the use of stimulants following paediatric ABI include the lack of long-term studies with appropriate power, study design and explicitly described randomisation procedures, and variable neuropsychological capture of attention. To enhance clinical assessment and to obtain improved outcomes for this group, it is recommended that high quality, well-designed level 1b randomised controlled trial (RCTs) with condition or injury mechanism specific paediatric samples are conducted to address study limitations and develop a diagnosis and treatment delineated evidence base.

To assist clinical endeavour in paediatric neurooncology, it will also be vital for studies to reduce heterogeneity by using samples that consist solely of children or injury mechanism specific paediatric ABI. The long-term effects of MPH will need to be monitored and investigated. If findings confirm the trend in the current evidence base of the short-term efficacy of MPH following paediatric ABI, there may be very significant implications for routine use of within-clinic screening measures for assessment, method of monitoring clinical effectiveness, prescribing practices in paediatric oncology and neurorehabilitation, and education and social functioning. In order to determine whether stimulants should be used after ABI, clinical practice must ensure routine scrutiny of cognition, particularly attention and scholastic outcomes. The online supplementary table is available online only. To view these files please visit the journal website (http://adc.bmj.com).

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Contributors All authors contributed to conception and design. EN contributed to the development of search terms and format of data retrieval. MM and DM-E contributed to the analysis and interpretation of extracted data and drafting of the article with critical revisions. Following liaison with DWH, EN and DM-E, MM gave final approval for the version to be submitted.

Competing interests None.

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Clinical bottom line

- Stimulants have been used in children with impaired attention and hyperactivity following acquired brain injury (ABI) with positive results. (Grade B)
- Teams treating paediatric ABI need to assess for the presence of inattention and consider the use of stimulants with individualised n-of-1 monitored trials. (Grade B)

REFERENCES

Question 3 Should stimulants be administered to manage difficulties with attention, hyperactivity and impulsivity following paediatric acquired brain injury?

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