Pharmacotherapy for treatment of attention deficits after non-progressive acquired brain injury: a systematic review

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CRD summary
This review concluded that there was a lack of robust evidence that medication improved attention after traumatic brain injury or stroke, but there was evidence of potential benefit for some patients and further research was warranted. In light of the heterogeneity between studies and a paucity of high-quality evidence, the authors' cautious conclusions are justified.

Authors' objectives
To evaluate the safety and effectiveness of medications used to improve attention in patients with non-progressive acquired brain injury.

Searching
MEDLINE, EMBASE, CINAHL and PsycINFO were searched for studies published between 1987 and 2008. Search terms were reported.

Study selection
Studies of medication used to improve attention deficits in adults over 18 years with new onset or previously acquired brain injury that resulted from trauma, cerebrovascular disease, hypoxia, infection, tumour, post neurosurgery or post radiotherapy were eligible for inclusion. Studies of patients with low arousal states, minimal conscious states and neurodegenerative diseases were excluded. Eligible studies needed at least one outcome that assessed attention or cognitive ability. Single case reports were excluded.

Included studies evaluated noradrenaline agonists, dopamine agonists or acetylcholine agonists in varying doses. Most patients had chronic or subacute traumatic brain injury. Other included patients had stroke or hypoxic brain injury. Attention was assessed using a range of standardised attentional and cognitive tasks, standardised scales of cognitive function, videotaped records and other caregiver and clinician rating scales.

The authors did not state how study selection was performed.

Assessment of study quality
Included studies were graded according to the level of evidence following guidelines for the management of severe head injury produced by the Brain Trauma Foundation. Two reviewers independently assigned the levels of evidence. Studies graded as level I were independently verified by a third reviewer.

Data extraction
The authors did not state how data were extracted for the review.

Methods of synthesis
The studies were combined using a narrative synthesis with results grouped according to medication type.

Results of the review
Twenty-six studies were included for review (n=497): 16 RCTs (n=361); one ABA design (n=10); three prospective studies (n=47); three case series studies (n=10); and three retrospective studies (n=69). Five studies were graded level I, 12 studies were graded level II and nine were graded level III.

Noradrenaline agonists (11 studies): Methylphenidate significantly improved speed of information processing, mental processing speed and attentiveness in two level I studies. A third level I study found no significant differences between groups for measures of attention. Results for level II studies of methylphenidate were mixed. One level III study showed
significant benefits of d-amphetamine on functional outcome.

**Dopamine agonists (10 studies):** Results for the effect of amantadine in patients with acquired brain injury were mixed. One level II RCT found significant benefits of amantadine on cognitive and functional outcome; however, another level II RCT found no significant differences between groups. One level III study reported significant benefit of Levodopa on neglect. Bromocriptine did not significantly improve attention compared to control in one level II study, although a level III study found significant benefits on neglect and inattention.

**Acetylcholine agonists (five studies):** Donepezil significantly improved information processing and sustained attention compared to controls in one level I study. Physostigmine and CDP-choline did not significantly improve memory or attention in patients with acquired brain injury compared to controls.

None of the studies was adequately powered to detect adverse events.

**Authors’ conclusions**
There was a lack of robust evidence that medication improved attention after traumatic brain injury or stroke. However, there was evidence of potential benefit for some patients and further research was warranted.

**CRD commentary**
The review addressed a clear question with well-defined inclusion criteria for intervention and patients. Inclusion criteria for study design and outcomes were broad. Several relevant databases were searched. The review appeared to be restricted to published studies, which introduced a risk of publication bias. It was unclear whether appropriate steps were taken to minimise language bias. No formal validity assessment beyond assignment to levels of evidence was conducted; therefore, it was not possible to be sure of the quality of included studies. It was unclear whether steps were taken to minimise reviewer error and bias in the study selection and data extraction processes. Most of the included studies were of lower levels of evidence. The authors noted that the findings may also be confounded by natural recovery or use of adjuvant behavioural therapies. The decision to combine the studies in a narrative synthesis was appropriate given clinical heterogeneity between studies. However, the absence of statistical data made it difficult ascertain the clinical and statistical significance of the findings. In light of the heterogeneity between studies and the paucity of high-quality evidence, the authors' cautious conclusions were justified.

**Implications of the review for practice and research**

**Practice:** The authors stated that methylphenidate can improve information processing speed in some patients following traumatic brain injury and there was weak evidence that dopamine agonists improved hemispatial neglect after stroke.

**Research:** The authors stated that further controlled studies were needed. Studies needed to identify specific deficits in attention or cognitive domains, assess risk and benefits on an individual subject basis, use appropriate outcomes with a priori success criteria defined through a functional goal setting process, record adverse events, provide clear definitions of treatment duration and concomitant behavioural therapy, evaluate patient and carer subjective ratings of the intervention and evaluate the impact of medication shortly after injury.

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