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Review Article

The effectiveness of dopamine agonists for treatment of neuropsychiatric symptoms post brain injury and stroke

Sami MB, Faruqui R. The effectiveness of dopamine agonists for treatment of neuropsychiatric symptoms post brain injury and stroke.

Objective: Traumatic brain injury and stroke are among the leading causes of neurological disability worldwide. Although dopaminergic agents have long been associated with improvement of neuropsychiatric outcomes, to date much of the evidence to date has been in case reports and case series or open label trials.
Methods: We undertook a systematic review of double-blinded randomised controlled trials (RCT) to determine the effect of dopaminergic agents on pre-defined outcomes of (a) apathy; (b) psychomotor retardation; (c) behavioural management and (d) cognitive function. Databases searched were: Medline, EMBASE, and PsychInfo for human studies. The Cochrane Clinical Trials Database and the TRIP Medical database were also searched. All identified studies, were further hand-searched.
Results: We identified six studies providing data on 227 participants, 150 of whom received dopaminergic therapy. Trials were compromised by cross-over design, inadequate wash out period, small numbers and heterogeneous outcome measures. However one good quality RCT demonstrates the efficacy of amantadine in behavioural management. One further RCT shows methylphenidate-levodopa is efficacious for mood post-stroke. One study shows rotigotine to improve hemi-inattention caused by prefrontal damage.
Conclusion: Our systematic review demonstrates an evolving evidence base to suggest some benefits in agitation and aggression, mood and attentional deficits. However, there are key limitations of the studies undertaken to date involving small numbers of participants, heterogeneous outcome measures, and variable study designs. There is a need for on-going large prospective double-blind RCTs in these medications using standardised criteria and outcomes to fully understand their effectiveness in this patient group.

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Summations

- Neuropsychiatric deficits are common and can be debilitating after brain injury and stroke.
- Accumulating evidence suggests a dopamine deficit post brain injury.
- This review of double-blind randomised controlled trials (RCTs) demonstrates accumulating evidence that dopaminergic medications may be beneficial in aggression and in mood post stroke.

Considerations

- A heterogeneity of outcome measures used in trials restricts ability to pool data.
- There are still a limited number of double-blind trials which have explored this area.
- Further RCTs of adequate methodological quality are needed.

Introduction

Traumatic brain injury (TBI) and stroke are among the leading causes of neurological disability and cognitive impairment worldwide. Ischaemic and haemorrhagic stroke cause 4.1% of all disability adjusted life years, and account for 4 346 000 years lived with disability (1,2); whereas 13 million people have TBI-related disability in Europe and the United States (3). Indirect and direct costs of these disorders are correspondingly high – with estimated total costs of $100.0–$151.8 billion upon the US economy (4).

The neuropsychiatric consequences of both traumatic and non-traumatic insults can be remarkably similar with depression, anxiety, marked cognitive impairment agitation and aggression, apathy, delirium-like states and very occasionally psychosis reported subsequent to both injuries (5,6). Typical mood and psychotic disorders, which develop subsequent to injury, can be managed by psychiatrists in a manner similar to their non-organic counterparts, however, no clear pharmacological strategy has yet been identified for the debilitating problems of apathy, psychomotor retardation, behavioural disturbance and impaired cognitive function. Thus the establishment of a clear evidence base in this regard would have implications for both psychiatric and rehabilitative follow-up of these patients.

Some evidence exists to suggest a dopamine deficit in brain-injured states. Animal models of induced cerebral ischaemia indicate large acute phase leakage of dopamine from the striatum into extracellular tissues (7,8). Similar evidence of striatal dopaminergic hypofunction has been demonstrated in TBI-animal models (9). Widespread disruption to dopamine transmission results across multiple pathways after brain injury (10). Animal models have also provided evidence that dopamine-based treatment can correct such deficits. Levodopa treatment has been demonstrated in animal models to improve functional recovery after stroke (11). The D-2 agonist, bromocriptine has also shown efficacy in sparing spatial memory loss in rodent models of head-trauma (12). Conversely dopamine antagonists such as haloperidol have been noted to impair recovery in brain injured animals (13). This suggests dopamine has an important role in modulating neuronal recovery after injury. These findings also translate to human experiments. Deficits of both dopamine 2 receptor (D2R) and dopamine active transporter (DAT) are demonstrated on imaging of brain injured patients compared with age and sex matched controls (14). A dopamine hypothesis has thus been proposed for the cognitive impairment resultant to brain injury (10).

Dopamine agonists have been reported to have positive effects in treating the neuropsychiatric sequalae of brain injury. One case series reported 19 out of 30 patients with severe head injury and aggression to respond to amantadine over the course of a year (15). Other case series have also shown positive response of cognitive function, attention and motivation in persons with head injury in the rehabilitative setting (16–18). Open label trials have shown improved neuropsychiatric outcomes in brain-injured patients with bromocriptine and amantadine (19,20). Case studies have also reported improvement with the use of dopaminergic therapy in patients with neuropsychiatric sequalae of stroke. A combination of carbidopa/levodopa and pergolide has been reported to substantially improve the outcome of post-infarct akinetic mutism (21). Ropinirole has been reported to have had a dramatic affect on post-stroke apathy (22).

However most of the reported associations to date have been limited by considerable methodological shortcomings. Case studies are anecdotal evidence, whereas larger case series may report improvement but are uncontrolled. This is critical in studies of neurological injury, where a degree of improvement may be expected by neuronal recovery over time. Similarly trials to date which have reported positive results have been open-label and consequently susceptible to placebo effect. Thus a systematic review of rigorous double-blind randomised controlled trials (RCTs) is needed.

This review was conducted to systematically review the evidence for dopamine agonists in stroke and head injury. We aimed to review studies of prospective double-blind RCTs on predefined neuropsychiatric outcomes.

Materials and methods

Inclusion/exclusion criteria

Inclusion criteria for studies were: (1) RCTs (2) double blinded (3) of dopaminergic therapy (4) looking at the outcomes of (a) apathy; (b) psychomotor retardation; (c) behavioural management and (d) cognitive function. For our purposes the control group could be

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placebo or alterative therapy; we accepted both papers using parallel group or cross-over design; and dopaminergic agents were defined as any anti-Parkinson's medication known to be pro-dopaminergic. Amphetamine and methylphenidate if given without other dopaminergic therapy were not included in this definition, although they are pro-dopaminergic, they have a profile as psycho-stimulant agents and work on them in brain injury has been undertaken elsewhere (23–25). Exclusion criteria was defined as (1) trials without a control group; (2) trials single blinded or un-blinded; (3) non-randomised studies; (4) trials where outcome was motor outcome or non-neuropsychiatric out-come; and (5) papers not in English.

Search strategy

The search for literature was undertaken on the 18th–21st December 2103. The search terms used were:

> ('bromocriptine OR cabergoline OR levodopa OR madopar OR ropinirole OR pramipexole OR sinemet OR amantadine OR apomorphine OR 'dopamine agonist') AND ('traumatic brain injury' OR 'head injury' OR 'brain injury' OR TBI OR stroke OR CVA OR 'cerebrovascular accident') AND (apathy OR avolition OR 'psychomotor retardation' OR behavior OR behavior OR agitation OR 'cognitive function' OR memory OR 'executive function' OR attention OR concentration)

Databases searched were: Medline, EMBASE, and PsychInfo for human studies. The Cochrane Clinical Trials Database (www.cochrane.org) and the TRIP Medical database (www.tripdatabase.com) were also searched using the same search terms. All identified studies, were further hand-searched for any other studies of interest.

Data extraction

Data extracted for each identified study included interventional agent and dose, control and dose, number of participants, age-range and inclusion and exclusion criteria for each study. Follow-up period of each study was extracted. Data were extracted separately for each of the four outcomes of apathy, psychomotor retardation, behaviour and neurocognitive measures including instrument and score. Because of the heterogeneity of outcomes and instruments used, no single measure could be used as a summary outcome measure across trials, instead data was extracted for instruments separately. Tolerability data were extracted in two ways (i) withdrawals/drop-outs due to suspected adverse effects and (ii) record of all adverse effects in trial participants.

Risk of bias

Selection of trials with adequate randomisation and blinding were used to minimise risk of allocation and measurement bias. In order to further ascertain systematic bias within trials we further extracted information on methodology (parallel group design, cross-over method, *n*-of-1 study); information on whether power calculation had been undertaken; whether intention to treat or on-treatment analysis was used and percentage lost to follow-up and whether this was stated. This was to gain information on risk of attrition bias and whether there was a possibility of Type II error in underpowered studies. In the case of cross-over trials we also extracted information on the stated washout period (if any), to determine whether data could be confounded by any possible carry-over effects. All included trials were scored using the Jadad score, a validated instrument to score quality of double-blind randomised controlled clinical trials (26).

Results

Study selection

The results of the search strategy can be seen in Fig. 1. In total 593 records were screened of which 20 papers were identified. Of these six studies were of adequate quality, looking at the identified out-comes. Four of these studies focused on TBI, whereas two focused on stroke. These provided data on 227 participants, 150 of whom received dopaminergic therapy: with 95 out of 133 TBI patients exposed and 55 out of 94 stroke patients receiving dopaminergic therapy. Medications trialled were amantadine in three trials; and bromocriptine, rotigotine and levodopa in one trial each. Characteristics of trials can be seen in Table 1.

We further present our results on each of the neuro-psychiatric symptom areas below:

Treatment of apathy

No identified studies looked directly at apathy. One study used the Geriatric Depression Score (GDS) to assess mood post stroke (27). The Geriatric Depression is not a direct marker of apathy, although it includes questions of withdrawal, apathy and lack of vigour and can provide indirect evidence of apathy. This was a multicentre study parallel groups design RCT which stratified 100 patients ranging from 15 to 180 days post ischaemic stroke into groups receiving levodopa, methylphenidate, methylphenidate and levodopa or placebo for 15 days. A total of 78 participants completed the study and on treatment analysis was undertaken. This showed the combined dopaminergic treatment (methylphenidate + levodopa) improved GDS

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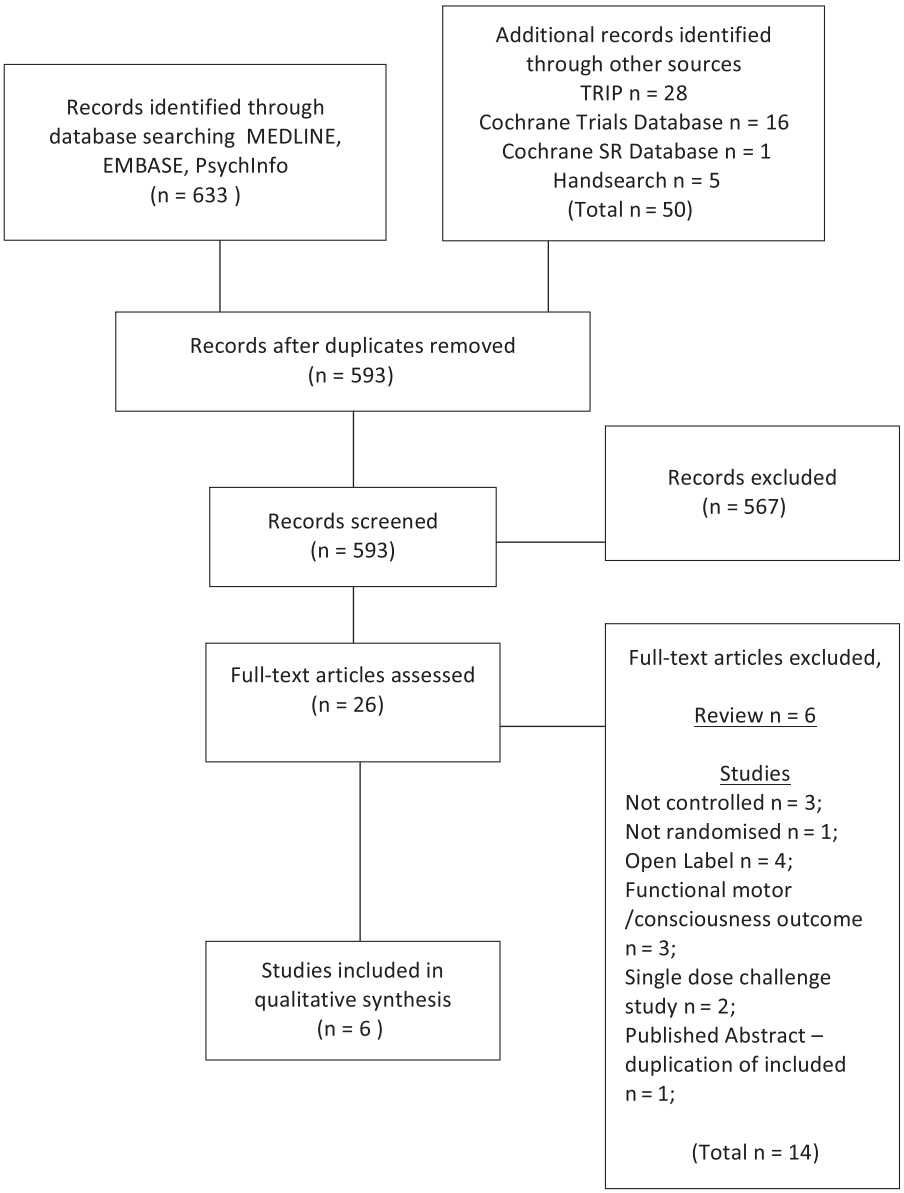

Fig. 1. Systematic review flow diagram.

scores significantly from the placebo treatment at 90 days and 180 days.

Treatment of psychomotor retardation

No identified studies looked at psychomotor retardation or its corollaries.

Behavioural management

Three studies looked at behavioural management in patients with TBI (28–30). All looked at similar doses of amantadine. Each trial used different outcome measures – the Neurobehavioural Rating Scale, the Agitated Behavioural Scale and the Neuropsychiatric Inventory – Irritability and Aggression subscales. The two older studies found no significant difference in measures between dopaminergic and placebo treated groups. However, they suffered from considerable methodological short comings including small sample size [($n = 10$) Schneider et al. (28); ($n = 35$) Meythaler et al. (29)] which may predispose to Type II error. Both studies were also not primarily of patients with agitation or behavioural disturbance – Schneider et al. selected patients with attention and concentration deficits (28), whereas mean agitation scores in the Meythaler et al. study were low at baseline (29). Both were on treatment analysis – with a high reported drop-out rate reported by Schneider et al. (45%) (28), with the drop-out rate of Meythaler et al., unreported (29). Furthermore in the Meythaler et al. study, there was no reported wash-out period in

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Table 1. Characteristics of included trials

Paper	Agent	Age	Population	Control	n	Follow-up period	Apathy	Psychomotor retardation	Behaviour	Neurocognitive	Conclusions
Schneider et al. (28)	Amantadine 50–150 mg bd	18–55	In patients with closed TBI	Placebo	10	2 weeks on AMH, 2 weeks wash out, 2 weeks on placebo			NRS	Orientation, memory, attention, executive	No significant findings. Inconclusive because of small sample size and high drop-out rate
Meythaler et al. (29)	Amantadine 100 mg bd	16–75	Severe TBI post RTA within 6/52. postulated diffuse axonal injury	Placebo	35	6 weeks on AMH, 6 weeks on placebo.			ABS	MMSE*, GOAT*, FIM-Cog	Consistent trend towards a more rapid functional improvement on AMH. AMH is safe in trial population
Whyte et al. (31)	Bromocriptine 5 mg bd	16–60	Closed moderate to severe TBI at least 3/12 before enrolment, attentional complaints	Placebo	12	4 weeks on bromocriptine, 4 weeks on placebo.				Attention	No evidence that bromocriptine improves attentional measures. Study limited by high drop-out rate and small sample size
Delbari et al. (27)	Levodopa 125 mg/day	Mean 64 ± 9.8	Ischaemic CVA, 15–180 days post injury	(1) Placebo, (2) MPH (3) LD + MPH	78	Treatment for 15 days. Follow up for 90 and 180 days	GDS*			MMSE	Combination of levodopa and MPH improves mood in post ischaemic stroke patients
Gorgoraptis et al. (32)	Rotigotine 9 mg patch/day	24–80	Right hemisphere stroke causing hemi neglect and left motor weakness	Placebo	16	Treatment for 7–11 days; follow-up approximately 38 days				MCT*, Corsi Blocks, VSVT*	Rotigotine significantly improves visual neglect. Not able to determine long-term benefits
Hammond et al. (30)	Amantadine 100 mg bd	16–65	>6 months post TBI	Placebo	76	28 days			NPI-I*; NPI-A*		Amantadine 200 mg daily appears a safe and effective means of reducing irritability and aggression among individuals with chronic TBI

ABS, Agitated Behavioural Scale; AMH, amantadine; CVA, cerebrovascular accident; FIM-Cog, Functional Independence Measure Cognitive Score; GDS, Geriatric Depression Score; GOAT, Galveston Orientation and Amnesia Test; LD, levodopa; MCT, Meseleum Cancellation Task, MMSE, Mini Mental State Examination; MPH methylphenidate; NPI-A, Neuropsychiatric Inventory Aggression; NPI-I, Neuropsychiatric Inventory – Irritability; NRS, Neurobehavioural Rating Score; RTA, road traffic accident; TBI, traumatic brain injury; VSVT, Visual Salience and Vigilance Task.

* Favours dopamine therapy.

the cross-over design, which may lead to carry-over effects of those who commence dopaminergic therapy into the placebo phase (29).

One larger ($n = 76$) well-designed parallel groups study of patients who were referred for irritability with moderate to severe TBI over 6 months in duration showed significant improvement in the dopaminergic group (30). There was a significant mean reduction of −4.3 in the dopaminergic group versus −2.6 on placebo Neuropsychiatric Inventory – Irritability scale and a reduction of 3 points in the dopaminergic group by 81% versus 44% in the placebo group. For patients who had baseline aggression alongside irritability there was a reduction in Neuropsychiatric Inventory Aggression subscale in the dopaminergic group versus the placebo group which was statistically significant. Consequently from this larger, more rigorous study there appears to be supportive evidence that amantadine has efficacy in treating chronic irritability and aggression in TBI.

Cognitive function

Three studies looked at cognitive function in patients with TBI (28,29,31), whereas two studies examined this for stroke (27,32).

Meythaler et al. in a placebo controlled 12 week cross-over trial of amantadine of patients with severe head injury found a trend to more rapid improvement on amantadine as opposed to placebo (29). However these results were not significant which maybe because of the moderate sample size of the study ($n = 35$) and the possible carry-over effects of active treatment into placebo phase. Similarly the other cognitive domains examined the Functional Independence Measure Cognitive Score which found a non-significant trend favouring dopamine therapy, whereas the Galveston Orientation and Amnesia Test showed no difference between groups (29).

Two further small studies also examined various cognitive measures after short courses of amantadine ($n = 10$) (28) and bromocriptine ($n = 12$) (31). Both found no significant differences in favour of dopamine therapy arm in various cognitive measures including measures of orientation, memory, executive function, flexibility, and attention (28) and various attention domains (31). These cross-over trials had considerable limitations with small sizes, on treatment analyses, a high drop-out rate (45%) in the amantadine trial (28), and considerable risk of selection bias in the bromocriptine trial with more than 1100 subjects screened to select the 12 participants (31).

Taken together from the current three double-blind randomised placebo controlled trials to date, there is no convincing evidence to show that cognitive function post TBI is improved with a course of dopaminergic therapy. However, these trials to date have been small, used an array of neuropsychological outcomes and further research is still needed in larger well-designed trials.

Delbari et al., in their parallel groups designed study of levodopa, methylphenidate, combination treatment and placebo in post-stroke patients, found no significant differences in the Mini Mental State Examination (MMSE) score between the groups (27). However, when the patients were grouped based upon the presence of depressive symptoms (GDS > 8) they found depressed patients to have significantly greater improvement in MMSE scores as the depression lifted (27). Given that this study also showed dopaminergic therapy to be associated with treatment of depression this suggests that dopaminergic agents may have a role in lifting the cognitive impairment associated with post-infarct depression.

Gorgoraptis et al. studied visual inattention in patients with hemi-neglect resultant to 16 mixed ischaemic and haemmorhagic strokes (32). They undertook an ABA '*n*-of-1' design of pre-treatment, treatment of rotigotine patch and post treatment in all patients in a randomised double-blinded manner. Treatment with rotigotine was associated with significant improvement in visual search using the Mesulam Shape Cancellation Task. However other measures did not pick this up on the Bells' Cancellation Task or Touch Screen Cancellation task which was postulated by the authors as due to the sensitivity of these tools. Performance on the Visual Salience and Vigilance Task also tended towards significant improvement during the dopaminergic phase of treatment. This effect was exacerbated when they considered those who had extensive prefrontal subgroup as against those who had minimal prefrontal damage (32). This trial suggests dopaminergic therapy to have a role in treatment of hemi-inattention due to cortical deficits. However, larger parallel groups double-blind RCTs are required to demonstrate the extent of this efficacy.

Tolerability and adverse effects

Extracted data on tolerability can be seen in Table 2. Amantadine was seen to be safe and tolerated at the low dosages it was employed (100–300 mg/day) with 2/83 (2.4%) exposed participants having to discontinue drug due it due to seizures in one case and rash in another. Only the larger trial reported a full formal adverse effects comparison between drug and placebo groups (30), but the other two smaller trials did not note any further instances of suspected adverse effects (27,28). The one trial that trialled bromocriptine found relative intolerability due to the medication at doses titrated upto 5 mg bd (29). In all, four participants out of the initial 22 (18%)

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Table 2. Tolerability data from included trials

Agent	Dose	*n* (exposed)	Exposure period	Withdrawal due to suspected AE	AE scale administered by group?	Other AE (including mild and self-limiting)	Comments
Amantadine (28,29,30)	50–150 mg bd	83	2–6 weeks	*n* = 2 1 rash (28) 1 seizure (30)	No (28) No (29) Yes (30)	No AE reported (28) No AE reported (29) ns difference between groups (30)	
Bromocriptine (31)	5 mg bd titrated	22*	4 weeks	*n* = 4(31) 1 hypotension 1 light headedness 1 vomiting 1 agitation	Yes (31)	No other differences placebo vs. bromocriptine (31)	
Levodopa (27)	125 mg/day	39†	15 days	None reported†	No (27)	'no negative side effects reported in any group' (27)	15/100 deaths due to CVA in trial. 7/100 further loss to follow-up. (27) Mortality not thought to be related to trial medication. No group comparison available.
Rotigotine (32)	9 mg patch/day	16	7–11 days	None	Yes (32)	Fatigue 4 (rotigotine) vs. 0 (placebo) Nausea 5 vs. 0 Vomiting 1 vs. 0, Diarrhoea 2 vs. 0	

AE, adverse effect; ns, no significant.
* Including loss to follow-up.
† Data not available for participants lost to follow-up.

discontinued the medication due to side effects of hypotension, light headedness, vomiting and agitation in one case each. Levodopa was reportedly well-tolerated with no serious adverse effects reported due to the medication, however this did not included patients lost to follow-up and a formal adverse effects scale was not reported (27). There were 15 deaths in the trial, which were reported as due to the initial stroke, but data regarding difference in mortality between drug administered and placebo groups was not reported upon. Rotigotine was well-tolerated in participants, however there was a higher incidence of gastrointestinal disturbance and fatigue in participants when administered the drug as compared with placebo (32).

Risk of systematic bias across all studies

Methodological assessment of trials is shown in Table 3. All trials were randomised double-blinded controlled trials with all having placebo arms and one trial having multiple treatment arms. However there were a variety of designs undertaken: 2/6 used parallel groups design, 3/6 used cross-over design while 1/6 used an ABA '*n*-of-1' study design. In general parallel groups allow for straightforward comparison between groups during both treatment and post-treatment phases. However for adequate randomisation they require larger groups, consequently both larger trials ($n = 76–78$) used this method while the others ($n = 10–35$) used alternative methods. These require more complicated statistical analysis to determine trends. Cross-over trials are particularly susceptible to carry-over effects of medication into placebo phase and only 1/3 cross-over designed trials included an adequate carry-over period (defined as five half lives of the active agent). There was also variability in the data analysis, with only 2/6 trials reporting intention to treat data and variation in attrition rates from trials reported from 0% to 44.4%. Trials were in general inadequately powered, with only 1/6 having undertaken a power calculation. Most trials performed well on the Jadad score with all but one scoring 3/5 or above.

Discussion

Although reviews on related topics have been undertaken before (23–25,33–35), this is the only paper to ensure that included trials are of double-blinded randomised controlled clinical trials. Consequently this is the most up-to-date paper looking at neuropsychiatric symptoms of TBI and stroke for dopaminergic agents in methodologically appropriate trials.

No medication to date has established unequivocal efficacy in the rehabilitation of neuropsychiatric

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Table 3. Methodological assessment of included trials

Paper	Agent	Methodology	Blinded?	Power calculation?	Data analysis	*n* (total)	*n* (lost to follow-up) (%)	Adequate washout period? (5 half-lives)	Jadad score	Comments/limitations
Schneider et al. (28)	Amantadine	Randomised, cross-over	Double	No	On treatment	10 (18 consented)	8/18 (44.4%)	Yes	3/5	High drop-out rate. acute effects of 2/52 AMH only
Meythaler et al. (29)	Amantadine	Randomised, cross-over	Double	No	On treatment	35	None stated	No	2/5	Short period of follow-up. Lack of significant findings may be due to Type II error. No comment on withdrawals
Whyte et al. (31)	Bromocriptine	Randomised, cross-over	Double	No	On treatment	12 (22 consented)	10/22 (45.5%)	No	4/5	More than 1100 subjects screened to select 12 participants
Delbari et al. (27)	Levodopa	Randomised, parallel	Double	No	On treatment	78 (100 consented)	22/100 (22%)	Not applicable	5/5	GDS is not a direct marker of apathy. MMSE insensitive for neurocognitive testing
Gorgoraptis et al. (32)	Rotigotine	Randomised, ABA design	Double	No	Intention to treat	16	0	No	4/5	n-of-1 design with interpatient variability
Hammond et al. (30)	Amantadine	Randomised, parallel	Double	Yes $n = 66$ for 80% power	Intention to treat	76	4 (5.2%)	Not applicable	4/5	Possible observer bias but NPI is validated tool

sequalae of TBI and non-TBI. A previous Cochrane Review included single-blind and double-blind randomised trials to establish pharmacological management of aggression and agitation in brain injury (34). The authors noted the lack of high-quality trials evaluating pharmacotherapy in this area. A significant advantage of β-blockers over placebo was identified. However this was based on two small studies requiring large doses of β-blockers and further replication in larger studies is required before efficacy can be decidedly established (34).

A major meta-analysis has been undertaken on variety of agents in early treatment, less than 7 days after injury including serotonergic and dopaminergic agents, calcium channel blockers, *N*-methyl D-aspartate antagonists, steroid treatment, peptide treatment, cannabinoids and free radical scavengers (35). Findings again were mixed. Arousal was noted to be markedly improved with amantadine and the bradykinin antagonist CP-0127 in early treatment. However, the amantadine data was based upon a single study which was retrospective and non-randomised (36) and the end cognitive effects of CP-0127 were noted to be small. A further meta-analysis by the same group in pharmacological management of patients with TBI in the post-acute period showed benefits of methylphenidate and amantadine in behaviour, donepezil for attention and memory and sertraline for cognition and psychomotor outcome (24). However, the quality of evidence left room for improvement – of the 30 trials examined across all medications in this review, only 10 were double blinded.

Stimulant medication has also been examined across both TBI and non-TBI (23). There is a mixed evidence base for the use of D-amphetamine and methylphenidate in cognition and mood. However this evidence has the same shortcomings of case studies and case series, low numbers in controlled trials and methodological issues.

Two reviews have examined the dopaminergic hypothesis. A non-systematic review examined amantadine for agitation and cognitive function in TBI (33). The found suggestions of efficacy but these were compromised by methodological shortcomings in the literature including the retrospective use of some trials, small numbers of participants and the heterogeneity of outcome measures used. A systematic review of dopamine agonists including methylphenidate was undertaken on TBI (25). The authors did not insist on double blinding nature of trials and found 20 RCTs, 14 of which were with methylphenidate, four of which were with amantadine and two were with bromocriptine. They were unable to come to firm conclusions because of identified heterogeneity of outcome measures, heterogeneity of the trial population and cross-over design studies without adequate wash-out period (25).

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They advised standardisation of trial criteria and the neuropsychological battery for implementation of the evidence base.

By ensuring the included studies were prospective, randomised and double blinded we have excluded important sources of bias which previous reviews have suffered from. This is particularly important in brain injury where placebo effects are demonstrably large (29,30) and neuronal recovery, especially early after impact of brain injury may be confounded for pharmacological mediated improvement. However, we also find important methodological impediments when assessing the quality of the evidence base. The small to moderately sized trials mean that most studies are underpowered and thus there is a risk of a Type II error. This is further compounded by the heterogeneity of outcome measures and thus a pooled meta-analysis is not possible. There are also important gaps in the evidence base. We pre-defined the symptom areas for review before commencing literature search and are surprised that there are no direct studies in either stroke or TBI evaluating the result of dopaminergic medication on apathy, given the widespread prevalence and debilitating effect of this in patients with either condition (37,38).

However, our review does demonstrate key features in the evolving evidence base. There is now a good-sized well-designed RCT demonstrating the efficacy of amantadine in behavioural management (30). Similarly a parallel groups multi-centre trial has provided evidence that dopamine therapy is efficacious for mood post-stroke (27). Another well-designed, albeit small study has provided preliminary 'proof of concept' data that dopaminergic therapy can improve hemi-inattention caused by prefrontal damage (32).

Explanations for these results can be considered. There is now accumulating evidence for the dopaminergic hypothesis of brain injury as discussed above (10). This describes hypo-functioning dopaminergic systems which may potentiate depression and irritability and are stabilised by administration of dopaminergic agents. Amantadine also has anti-*N*-methyl-D-aspartate activity which may also modulate glutamate induced excito-toxicity post injury (33). Rotigotine, used in the inattention study, is a preferential D1 agonist and D1 receptor activity in the prefrontal cortex has been noted in animal models to predict cognitive ability (39). Further studies in persons with TBI and non-TBI are needed to further explore this area.

Limitations

We do find limitations in our work. As discussed the quality of studies, especially those using cross-over designs and having inadequate wash-out periods; the heterogeneity of outcome measures; the small numbers of participants all compromise the evidence base. Furthermore our review is of English only studies and of only published date which may predispose to a publication bias. We only looked at pre-defined neurocognitive symptoms, whereas other studies have demonstrated improved functional motor outcome with dopaminergic therapy but this was outside the scope of our review (40). Similarly we did not assess measures of arousal post TBI, or overall levels of physical disability as they fell outside the scope of this study.

Conclusion

There has been longstanding evidence that dopaminergic therapy improves neuropsychiatric outcomes in TBI and non-TBI. However, until recently there has not been rigorous evaluation of this in randomised double-blinded controlled clinical trials. Our systematic review demonstrates an evolving evidence base to suggest some benefits in agitation and aggression, mood and attentional deficits. However, there are key limitations of the studies undertaken to date involving small numbers of participants, heterogeneous outcome measures, and variable study designs. There is a need for ongoing large prospective double-blind RCTs in these medications using standardised criteria and outcomes to fully understand their effectiveness in this patient group.

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Conflicts of Interest

The authors declare no conflict of interest.

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