Does amantadine maintain function in long-established brain injury? A single case experimental design.

FitzGerald A, Main L¹, McNicholl U¹, Foggo J², Rowney F³, Haire N⁴, McLean R¹
1 NHS Lothian, Astley Ainslie Hospital, Edinburgh Lothian, Scotland
2 Case Management Services Ltd, Edinburgh Lothian, Scotland
3 Balanced Movement, Edinburgh Lothian, Scotland
4. Queen Margaret University, Edinburgh; The University of Edinburgh

Abstract

Research into the role of dopamine agonist (DA) use in acquired brain injury (ABI) has primarily identified roles in restoration of consciousness and cognition in the acute or recovery phase following injury (1-5). The role of DA in later functional recovery is less well defined. We report a single case experimental design (SCED) demonstrating amantadine associated functional improvement, six years following severe TBI. Upon recruitment, the patient had been prescribed amantadine for the previous two years based on reported subjective improvement. This trial was devised as a means of justifying continued use.

A scoring system was developed based on established abilities in managing of personal care and social interaction. Specific tasks were identified within which up to 7 component actions were identified, with 34 actions described in total. Each component action was graded on a ranked scale of 1 to 4 to based on quality of response to a given request, or the extent of prompting required to elicit response. Using a SCED format, actions were scored at baseline while continuing with amantadine use, and at intervals following withdrawal, and reintroduction. Daytime sleep duration was also recorded.

At 3rd and 5th weeks post withdrawal, deterioration was recorded in 27 of the 34 graded activities. At 3rd and 5th weeks following reintroduction, all but 3 actions were graded at baseline or higher. Duration of afternoon sleep increased from 35 minutes to 80 minutes during the trial withdrawal period returning toward baseline on resumption of amantadine.

This outcome supports a view that amantadine may have a role in sustaining long-term functional benefit following severe TBI. The model used suggests potential to use similar client specific measures of outcome in an SCED model as a template to capture change in a larger scale trial.

Introduction

Acquired brain injury (ABI) is a major cause of morbidity and mortality (Lawrence et al., 2016). In 2016-2017 there were 531 admissions per 100,000 of the population for all types of ABI in the UK which is a 10% rise since 2005-2006 (Headway, 2018). ABI includes traumatic ischaemic, haemorrhagic, infective, and anoxic brain injury. It can result in long term physical, cognitive and communicative disability as well as impairments with psychological and social function (Ter Mors et al., 2019). Cognitive impairment can include low arousal; impaired attention, concentration and recall; and emotional impairments that
impact on initiation, mood, and behavioural regulation. These combine to have a negative impact on independent functioning, quality of life and care giver wellbeing (Leone & Polsonetti, 2005; Ter Mors et al., 2019)(Menon & Bryant, 2019).

It’s recognised that the management of ABI requires multidisciplinary specialist input but, with regards to the optimal pharmacotherapy to support recovery and enhance function, there is insufficient evidence to establish clinical guidelines (Talsky et al., 2011). Through its impact on dopamine and N-methyl-D-aspartate (NMDA) related pathways, amantadine may have neuroprotective roles (Meythaler, Brunner, Johnson, & Novack, 2002), promote functional recovery in brain injury (Chang & Ramphul, 2020), and enhance arousal, attention and executive functioning due to effect in the fronto-cortico-striatal loop (Kraus & Maki, 1997). Reports to date, demonstrate potential benefit in intensive care and early rehabilitation settings both in terms of increased arousal or restoration of function (Giacino et al., 2012a; Karli et al., 1999; Reynolds, Rittenberger, & Callaway, 2013; Schneider, Drew-Cates, Wong, & Dombovy, 1999; Whyte et al., 2005; Williams, 2007). Studies directed at demonstrating benefit in late recovery phase provide less evidence and are typically limited to single case reports (Arciniegas, Frey, Anderson, Brousseau, & Harris, 2004; Beers, Skold, Dixon, & Adelson, 2005; Kraus & Maki, 1997; Schneider et al., 1999). Amantadine has been associated with seizure risk, mood change, delirium and ataxia (Chang & Ramphul, 2020; Ter Mors et al., 2019), making it difficult to justify long-term use in a patient group in which the risk of seizure is increased and for whom communication impairments limit the ability to identify mood-related side-effects.

Following ABI, patients have a range of social, cognitive and physical impairments, with variations in severity in each. ABI is rendered more complex by the interdependence of impairments, recovery in one domain being influenced by ability to recruit abilities in others. This creates a challenge in identifying an outcome measure that is sufficiently sensitive and specific to quantify change across the range of cognitive and physical domains. Thus, while there is theoretical and some subjective basis for suggesting a role for amantadine in improving function, to date there is a lack of compelling evidence to date to demonstrate effectiveness (Chang & Ramphul, 2020; Edby, Larsson, Eek, von Wendt, & Ostergård, 1995; Okigbo et al., 2019).

A single case based analysis by Edby et al was able to demonstrate a small but definite improvement in the use of amantadine in a chronic ABI patient (Edby et al., 1995). A further systematic review by Ter Mors et al concluded that future studies into amantadine in the heterogenous ABI population should be in the format of Single Case Experimental Designs (SCEDs) and focus on the effects of treatment on participation and quality of life (Ter Mors et al., 2019). A SCED provides opportunity to use patient specific scaling to show measurable benefits from amantadine use. We describe use of this approach in an individual six years following injury. This study aims to examine the method used, and its potential as a template in comparable case studies.
Case Report

The patient, a 65-year-old male, sustained a traumatic brain injury (TBI) following a road traffic accident. He remained in a state of low awareness state from which he emerged over an 18 months period, recovering to an extent of visually fixing and following, transferring with stand-aid and feeding himself when handed food. Communication was limited to reflexive utterances, affectionate gestures, inconsistency in using yes/no responses or following one-part commands.

After a reassessment of level of awareness, he was prescribed amantadine at doses of 100mg twice daily, and made further gains including participation in personal care, vocalising basic needs, and giving appropriate single word responses to questions. Cessation of amantadine resulted in return to his 18-month baseline on each occasion. Trials with methylphenidate or modafinil were not associated with benefit. He also had a co-existing limb tremor and perioral dystonia which was unresponsive to amantadine or any other trialled medications.

The periods of amantadine administration were complicated by worsening of his TBI-related generalised motor seizures, resulting in increased frequency and duration. It was agreed by clinicians and patient’s family that treatment benefit outweighed this adverse effect. Increased anticonvulsant doses were associated with increased sedation or reduced function. Various combinations of anticonvulsant medications with amantadine 100mg twice daily were trialled until it was identified that combination with lamotrigine 150mg twice daily appeared to achieve the optimal balance in limiting seizure frequency to less than 4 per annum, and reducing seizure duration either to self-limiting or to being responsive to single-dose buccal midazolam.

Given the continuing need for anticonvulsant medication, and the absence of published evidence to support continued use of amantadine in ABI it was felt necessary to identify objective criteria for confirming benefit for this patient. As his established clinical baseline was now one of continued administration of amantadine, a reversal ABA format, non-blinded, SCED study based on a trial of treatment withdrawal rather than one of treatment initiation, was selected as the most appropriate means of testing benefit.

As there was no recognised outcome measure appropriate to his specific circumstance, a patient specific scale was designed to measure benefit in an objective format. Representative activities that were the focus of recent therapy interventions were identified by his occupational therapist; physiotherapist; speech therapist; music therapist; and rehabilitation physician. His partner who was his appointed guardian, provided consent, and contributed to trial design and implementation.
Methods
Specific tasks were identified, some of which required sequential completion of a series of component actions. These included personal activities of daily living including dressing, personal hygiene, eating, mobilisation; and social activities including communication and musical interaction. Within these, 34 specific actions were described, each graded on a scale of 1 to 4. Grading was defined in most actions by the extent of prompting required to complete the action using the following template.

1. Patient unable to attempt the action unassisted
2. Patient requires either repeated verbal prompts or augmentation of prompt by demonstration of technique, to complete action.
3. Patient requires just a single verbal prompt to complete action
4. Patient initiates or completes action in response to standard cues without need for added prompt.

Those actions that could not be graded based on requirement for prompt, were graded instead by duration or intensity of response generated in each action.

Table 1 attached describes these actions and grades.

INSERT TABLE 1 HERE

In the pre-trial phase the graded actions were practiced under partner or therapist supervision to ensure consistency in performance and interpretation, and to minimise potential for task learning effect during the course of the trial. Trial was conducted at a time of relative clinical stability. Patient was seizure free for the full duration of the trial period and did not experience any inter-current illness or disruption to usual routine.

Once consistency was established, amantadine was withdrawn in 100mg per day increments at weekly intervals and then omitted for a period of five weeks. It was then recommenced by increasing in 100mg increments at weekly intervals to restore dose at 100mg twice daily.

Graded actions were scored within five data point ranges as outlined below, by the therapist whose discipline was most appropriate to each task. Therapy visits were scheduled to minimise fatiguing effect of multiple assessments. In order to minimise disruption to patient, to ensure consistency in timing of assessments, and to enable trial to reflect real circumstances, assessments were performed in his own home. The logistics of achieving all of the above criteria impacted on ability to match assessment dates to intended dates. Therefore, actual interval ranges for assessments varied slightly from intervals intended to coincide with 3rd and 5th weeks following amantadine withdrawal and at 3rd and 5th weeks following reintroduction, as in Table 2: -

INSERT TABLE 2 HERE

Impact on daytime arousal was also assessed by measuring daytime sleep duration. This was documented by his partner, checking at 5-minute intervals, on successive days for five days at a time, at baseline, and at 3rd and 5th week intervals described above.
Results
There were 4 predefined actions which were not achieved unassisted by the patient in the pre-trial phase, and were graded at 1 at baseline. This meant that a drop in performance could only become identifiable in 30 of the 34 actions. Results are summarised in Figure 1 & 2.

Functional Assessment – Mean Scores
Mean grade for individual actions, at baseline was 3.3, median grade was 4.

At 3rd and 5th weeks following cessation of amantadine, mean grade dropped to 2.3 and 2.1 respectively in, with median grade of 2 in both intervals. A grade drop was documented in 27 of the 30 actions in which a drop in performance could be demonstrated. A grade drop of 2 was documented in 18 of the actions.

At 3rd and 5th weeks following re-introduction of amantadine mean grades improved to 3.4 and 3.5 respectively, with median grade of 4 in both intervals. Mean grades returned to baseline level in 21 actions, exceeded baseline in 8, and were less than baseline in 3 actions.

A comparison of the relative proportions of grades at baseline and at subsequent trial stages using Chi-squared analysis demonstrates the impact of amantadine in a more comprehensive way.

At baseline he achieved grade 1 in 4 actions; grade 2 in 1; grade 3 in 10; and grade 4 in 19. By the 5th week following amantadine cessation, the numbers in each corresponding grade category were significantly lower with grades 1 to 4 respectively achieved in 9; 13; 10 and 2 actions ($X^2 = 25.97$, $p < .01$). There was a smaller but comparable difference between grade spread relative to baseline at 3rd week following cessation ($X^2 = 16.92$, $p < .01$)

In 5th week following re-introduction of amantadine, he achieved grades 1 to 4 respectively in 3; 2; 4 and 25 actions which was a significant improvement in grade spread relative to that documented above for 5th week post cessation ($X^2 = 33.23$, $p < .01$). There was a similar difference in grade spread when comparing 3rd weeks post cessation with 3rd week following re-introduction ($X^2 = 21.42$, $p < .01$).

Functional Assessment – Composite Scores
At baseline cumulative total of individual grade values was 112.

At 3rd and 5th weeks following cessation of amantadine, cumulative scores had dropped to 78 and 73 respectively.

At 3rd and 5th weeks following re-introduction of amantadine cumulative scores increased to 117 and 119 respectively.

Learning (or Testing) Effect of Repeat Assessments
Though actions were practiced several times in advance of trial to eliminate potential for learning effect during the trial, there still appears to have been some learning effect with improvement in grade spread. Grades 1 to 4 were achieved in 4; 1; 10; & 19 actions respectively at baseline and in 3; 2; 4; & 25 actions...
respectively at 5th week following amantadine reintroduction, though this was not statistically significant ($X^2 = 3.87, p = .28$).

**Daytime Sleep Duration**

A period of afternoon sleep occurred on each day throughout the trial. Baseline afternoon sleep mean duration was 33 minutes (*median 35, standard deviation 10.4*) based on recordings over 5 successive days in the pre-trial phase.

During the amantadine withdrawal phase, mean sleep duration increased to 75 (Mdn 75, SD 30.7) and 79 (Mdn 75, SD 27.5) minutes respectively from days 19-23 and days 37-41 post-cessation. Comparison using students-t test suggested that the increase in sleep duration following amantadine cessation were significantly different both at 3rd weeks ($t = -2.96, p < .05$), and 6th weeks post-cessation ($t = -3.50, p < .05$).

After reintroducing amantadine mean sleep duration reduced to 43 (Mdn 30, SD 21.4) and 39 (Mdn 40, SD 10.8) minutes respectively from days 22-26 and days 34-38. This duration was greater but not significantly different relative to baseline sleep duration. The reduction relative to the period of amantadine withdrawal was significant when comparing the 5th week post cessation to 5th week post reintroduction ($t = 3.03, p < .05$), though this difference was less evident when comparing 3rd week post cessation to 3rd week post reintroduction ($t = 1.97, p = .084$).

**Adverse effects**

There were no new adverse effects either during withdrawal or re-introduction phases. The patient was well and remained seizure free for the duration of the trial.
Discussion

Amantadine was initially developed as an antiviral agent but is no longer used for this purpose. Its main uses are in Parkinson’s disease and fatigue management in multiple sclerosis (Chang & Ramphul, 2020).

The role of amantadine as a dopamine agonist is well established (Chang & Ramphul, 2020; Karli et al., 1999; Kraus & Maki, 1997; Meythaler et al., 2002). It facilitates dopamine release and delays dopamine reuptake and also has N-methyl-D-aspartate (NMDA) receptor antagonist effects which may contribute to a neuroprotective role (Meythaler et al., 2002; Talsky et al., 2011; Ter Mors et al., 2019). Amantadine is water soluble and is capable of crossing the blood brain barrier (Nickels, Schneider, Dombovy, & Wong, 1994). Anatomical studies have demonstrated its predominance in frontal lobe functioning (Karli et al., 1999; Leone & Polsonetti, 2005; Nickels et al., 1994).

Although data is limited, initial studies have suggested that it may promote functional recovery in brain injury (Chang & Ramphul, 2020). The impact is most notable in cognitive domains of arousal, attention and executive functioning due to effect in the fronto-cortico-striatal loop (Kraus & Maki, 1997). Reports to date, demonstrate potential benefit in intensive care and early rehabilitation settings both in terms of increased arousal or restoration of function (Giacino et al., 2012a; Karli et al., 1999; Reynolds, Rittenberger, & Callaway, 2013; Schneider, Drew-Cates, Wong, & Dombovy, 1999; Whyte et al., 2005; Williams, 2007). It’s suggested in particular to have a role in prolonged disorders of consciousness (Giacino et al., 2012b; McMahon, Vargus-Adams, Michaud, & Bean, 2009; Whyte et al., 2005).

Studies directed at demonstrating benefit in late recovery phase provide less evidence and are typically limited to single case reports (Arciniegas, Frey, Anderson, Brousseau, & Harris, 2004; Beers, Skold, Dixon, & Adelson, 2005; Edby et al., 1995; Karli et al., 1999; Kraus & Maki, 1997; Schneider et al., 1999; Ter Mors et al., 2019).

The evidence for its use is also limited particularly in the longer term and therefore careful consideration needs to be given in balancing any perceived benefits against potential side effects. It is difficult to justify long-term use in a patient group in which the risk of seizure or ataxia is increased and for whom communication impairments limit the ability to identify delirium or mood-related side-effects (Arciniegas et al., 2004; Beers et al., 2005; Chang & Ramphul, 2020; Karli et al., 1999; Kraus & Maki, 1997; Schneider et al., 1999). Published SCEDs have shown a small but definite improvement in the use of amantadine in chronic ABI and allows for the use of patient specific scaling to demonstrate benefit (Ter Mors et al., 2019).

SCED Format

While it is recognised that this potential exists, it has proven difficult to confirm this, and it has been suggested that a SCED trial format may be the most effective way of achieving this (Ter Mors et al., 2019). To date those that involved case series appear to have had inconclusive outcomes. Exceptions to this include trials by Beers and Kraus (Beers et al., 2005; Kraus & Maki, 1997). We believe that the trial design described may form a template for others to consider in similar circumstance.

The relative merits of SCED, and the degree of rigour required in design are already described (Lobo, Moeyaert, Baraldi Cunha, & Babik, 2017; Tate et al., 2016). Aside from overcoming challenges that arise
when recruitment opportunities are limited, SCED allows patient to serve as their own comparison within the trial which controls for many confounding variables, in particular demographic variables and the impact of concurrent interventions (Lobo et al., 2017). SCED format allows for meaningful outcome templates specific to the individual undergoing trial rather than generic parameters that accommodate whole group variations without representing true performance of any one individual (Lobo et al., 2017).

A primary advantage to SCED is to enable researchers in clinical settings who may have limited access to monetary, time, or personnel resource (Lobo et al., 2017). This trial required considerable personnel resource in terms of 5 clinicians, who within the course of their normal clinical role were enabled to provide time to identify realistic goals, train the patient, and then record each of 34 different clinical parameters in each phase of the trial, over a 14-week time period. To ensure consistency in application, and maximise patient performance, all assessments were trained and assessed in the patient’s home environment, rendering the tasks more relevant to the patient.

A withdrawal/reversal design typically includes two treatment cycles in ABABA pattern (Tate et al., 2016). We used a single ABA cycle in part to mitigate for the personnel resource requirement, but principally because the outcome of the first trial was so compelling in terms of the scale of change noted, that it was considered inappropriate to perform a second cycle when it was evident that there was no potential benefit to the patient to doing so.

It’s recommended that an SCED trial involves data collection at five points in each cycle (Tate et al., 2016). Given the scale of assessments performed, it was not feasible to justify this time commitment. However, we believe that the volume of data collected at the two data points in at B and A2 phases of the cycle provide comparable rigour in assessment and compensate for the reduction in the frequency at those phases.

Relevance of Outcome Measures

The heterogenic clinical pattern in TBI requires an outcome measure that spans the potential range of functions affected, such as Disability Rating Scale or the Functional Assessment Measure (L Turner-Stokes, Nyein, Turner-Stokes, & Gatehouse, 1999; WRIGHT, 2000), neither of which is sufficiently sensitive to measure the gains we describe. The template used in this trial uses a similar approach to those measures but the use of patient specific scales enables measurement in precise terms the meaningful change that this patient exhibited, to extent of identifying change in 34 of the 41 parameters. Goal attainment scaling is a well-established patient specific approach to outcome measurement, and may have been considered appropriate for this trial but use of GAS would also be limited by the patient’s cognitive inability to set their own goals (Lynne Turner-Stokes, 2009).

Data was recorded at a single point in the A1 phase, which represented the patient’s plateau in performance following re-iteration of the tasks in the weeks pre-trial, but it is recognised that the it may have been appropriate to measure at two separate data points to confirm this plateau, and limited likelihood that further learning would be a confounder.

At what was considered to be baseline, the patient had achieved the highest grade 4 at least once in 19 of the 34 component actions. This created a ceiling effect that limited the potential to confirm presence
or absence of learning effect. If one discounts the 18 component actions in which ceiling effect was achieved at both baseline and final datapoint, grades increased in 8 of the remaining 16 actions, and dipped in 2 ($\chi^2 = 7.55, p = .056$). Thus, while having baseline values that were at the top of the scale in many parameters served to accentuate the scale of difference following treatment withdrawal, we have not been able to definitively confirm that we achieved minimising of learning effect as a confounder.

**Trial of Withdrawal**

This was in effect a trial of treatment withdrawal rather than treatment initiation. In the context that informal pre-trial evidence suggested benefit from amantadine, a prolonged “wash-out” period to define an amantadine-free baseline after eliminating learning effect, could not be justified in the patient’s interests. Constructing this as a trial of withdrawal allowed the baseline to be more efficiently established as part of the patient’s ongoing rehabilitation.

**Blinding**

Conducting a single patient trial in a domiciliary setting over a 14-week period limited the potential to use placebo and/or blinding. It is unlikely that blinding would have avoided observer bias as it would not eliminate the potential for subjectivity in reporting the scale of any change noted. We believe that the number of measures used, the objective and precise nature of their description, the avoidance of inter-observer variation and the use of skilled therapists to record data limited the potential for observer bias.

**Dosing**

Amantadine is licenced to be prescribed in total daily dose of 400mg, but in view of the patient’s seizure history we decided to prescribe at a lower effective dose. A higher dose may have demonstrated greater effect, but this does not negate the evidence identified in this trial.

**Sleep Duration**

Although many trials refer to increased arousal in terms of activity, we are not aware of any trial that describes arousal in terms of sleep duration. Afternoon sleep duration was a secondary outcome recorded during the study. It is feasible to record this more reliably than is the case for overnight sleep duration. The use of sleep actigraphy is now considered to be the gold standard in sleep studies (Marino et al., 2013). A sleep diary has large potential for observer error. In this instance potential for error may have been compensated for by rigorous adherence on behalf of the patient’s partner, but such adherence could be in turn interpreted as indicating increased potential for observer bias.
Conclusion
Allowing for the limitations described, we believe this study adds to the evidence for benefit from amantadine following brain injury, but emphasising the less well described benefits in later phases of recovery. This is the first described case in which the dose response effect has been so clearly described, but it is hoped that the greater impact of this study will be achieved if the template used can be reproduced in other clinical trials.

Written informed consent for publication of their details was obtained from the patient/study participant and their guardian.
References


Figure 1: Mean grades following amantadine cessation and renewal, compared to pre-trial baseline with amantadine.
Figure 2: Cumulative total of grades for individual tasks after cessation and restarting amantadine 200mg/day

<table>
<thead>
<tr>
<th></th>
<th>Baseline assessments</th>
<th>23.7 (±6.9) days post cessation</th>
<th>36.2 (±1.6) days post cessation</th>
<th>16.9 (±3.0) days after restart</th>
<th>31.8 (±3.8) days after restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>112</td>
<td>78</td>
<td>73</td>
<td>117</td>
<td>119</td>
</tr>
</tbody>
</table>

Mean interval (and standard deviation) from baseline to assessment date
Table 1. Abbreviated description of activities and component actions
<table>
<thead>
<tr>
<th>TASK</th>
<th>Component actions</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRESSING UPPER/HALF</td>
<td>Choose from two shirts</td>
<td>Unable to choose</td>
<td>Repeated verbal prompt</td>
<td>Requires 2nd verbal prompt</td>
<td>Seeks with no further prompts</td>
</tr>
<tr>
<td>DRESSING UPPER/HALF</td>
<td>Choose a shirt/sweater</td>
<td>Unable to choose</td>
<td>Needs closed questions</td>
<td>Needs open question</td>
<td>Seeks spontaneously</td>
</tr>
<tr>
<td>DRESSING UPPER/HALF</td>
<td>Lift shirt to pull on</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>DRESSING UPPER/HALF</td>
<td>Place garment on shoulder</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>DRESSING UPPER/HALF</td>
<td>Pull garment over head</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>DRESSING UPPER/HALF</td>
<td>Adjust garment</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>DOMINATING GLASSES</td>
<td>Gafas when held in front of him</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>BRUSHING TEETH</td>
<td>Places on a toothbrush</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>DRINKING</td>
<td>Point to choice of cup or juice</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>DRINKING</td>
<td>Swallows offered drink</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>STAND AND WALK</td>
<td>Rubs hands and backs positioning</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>STAND AND WALK</td>
<td>Folds hands onto waist</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Single verbal prompt</td>
<td>Initiates task independently</td>
</tr>
<tr>
<td>STAND OR WALK</td>
<td>Dressing with visual aid</td>
<td>Unsuccessful attempt</td>
<td>Requires step to complete posture OR regular belt slipping</td>
<td>Repeated prompts OR 1-2 words OR shorter step with right foot</td>
<td>Achieved</td>
</tr>
<tr>
<td>WHEELCHAIR CONTROL</td>
<td>Controls brakes &amp; prepares</td>
<td>Assistance required</td>
<td>Augmented verbal prompt</td>
<td>Repeated prompt for any stage</td>
<td>One prompt for each stage</td>
</tr>
<tr>
<td>MUSIC VOCALIZATION</td>
<td>Volume of vocalization</td>
<td>No successful attempt</td>
<td>Whisper</td>
<td>Clearly audible</td>
<td>Loud</td>
</tr>
<tr>
<td>MUSIC VOCALIZATION</td>
<td>Sustaining vocal sound</td>
<td>No successful attempt</td>
<td>&lt;2 sec</td>
<td>2-3 sec</td>
<td>&gt;3 sec</td>
</tr>
<tr>
<td>MUSIC VOCALIZATION</td>
<td>Contributing to known song</td>
<td>No successful attempt</td>
<td>1 word with verbal musical prompt</td>
<td>&gt;1 word with verbal musical prompt</td>
<td>&gt;1 word with verbal musical prompt only</td>
</tr>
<tr>
<td>MUSIC VOCALIZATION</td>
<td>Reading</td>
<td>No successful attempt</td>
<td>Requires verbal musical prompt</td>
<td>Requires verbal musical prompt</td>
<td>Requires verbal musical prompt</td>
</tr>
<tr>
<td>MUSIC VOCALIZATION</td>
<td>Reading for drums and plays</td>
<td>No successful attempt</td>
<td>1-3 beats on verbal musical prompt</td>
<td>&gt;3 beats on verbal musical prompt</td>
<td>&gt;3 beats on verbal musical prompt only</td>
</tr>
<tr>
<td>AUDIO COMPREHENSION</td>
<td>Answers 10 questions on passage</td>
<td>No successful attempt</td>
<td>0-6 answered</td>
<td>6-10 answered</td>
<td>&gt;10 answered</td>
</tr>
<tr>
<td>WRITTEN COMPREHENSION</td>
<td>Answer 6 questions on passage</td>
<td>No successful attempt</td>
<td>1-2 responses correct</td>
<td>3-4 responses correct</td>
<td>&gt;4 responses correct</td>
</tr>
<tr>
<td>VOCATIONAL AWARENESS</td>
<td>Repeated with verbal sentence</td>
<td>No successful attempt</td>
<td>1-2 words audible</td>
<td>3-5 words audible</td>
<td>&gt;5 words audible</td>
</tr>
<tr>
<td>VOCATIONAL CLARITY</td>
<td>Repeating 6 word sentence</td>
<td>No successful attempt</td>
<td>1-2 words clear</td>
<td>3-5 words clear</td>
<td>&gt;5 words clear</td>
</tr>
<tr>
<td>VERBAL EXPRESSION</td>
<td>Response to standard question</td>
<td>No successful attempt</td>
<td>Single word responses</td>
<td>Multiple word responses</td>
<td>Unprompted spontaneous phrases</td>
</tr>
</tbody>
</table>
Table 2. Trial schedule specifying anticipated and actual timing of trial phases.

<table>
<thead>
<tr>
<th>Table 2. Trial Schedule</th>
<th>Planned Schedule (day number/s)</th>
<th>Implemented Schedule (day number/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline task assessment (A1) completed &amp; Amantadine cessation commenced</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Amantadine cessation completed</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Task assessment (B₃): 3rd week following amantadine cessation</td>
<td>28 - 34</td>
<td>28 - 41</td>
</tr>
<tr>
<td>Task assessment (B₃): 3rd week following amantadine cessation</td>
<td>42 - 48</td>
<td>47 - 52</td>
</tr>
<tr>
<td>Amantadine restarted at 100mg daily</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Amantadine increased to 100mg twice daily</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Task assessment (A₂₃): 3rd week after amantadine dose restoration</td>
<td>77 - 83</td>
<td>78 - 86</td>
</tr>
<tr>
<td>Task assessment (A₂₃): 5th week after amantadine dose restoration</td>
<td>91 - 97</td>
<td>92 - 101</td>
</tr>
</tbody>
</table>
KEY DATES – NOT FOR PUBLISHING
RTA 240310
Rehab adm 140510
RHND 210710
Lothian 171111