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Routledge
Taylor & Francis Group

Neuropsychological Rehabilitation

An International Journal

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/pnrh20

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To cite this article: Peggy Spauwen, Bert Ter Mors, Peter van Harten, Anne-Fleur Domensino, Rudolf Ponds & Caroline van Heugten (2020): Efficacy and safety of amantadine as a treatment for apathy after brain injury: Two single-case experimental design studies, Neuropsychological Rehabilitation, DOI: 10.1080/09602011.2020.1842214

To link to this article: https://doi.org/10.1080/09602011.2020.1842214

Published online: 30 Nov 2020.

NEUROPSYCHOLOGICAL REHABILITATION
https://doi.org/10.1080/09602011.2020.1842214

Efficacy and safety of amantadine as a treatment for apathy after brain injury: Two single-case experimental design studies

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ABSTRACT

Studies on the efficacy of amantadine as a treatment for apathy after brain injury are scarce and of low quality. We examined the efficacy and safety of amantadine for treatment of apathy in two individuals with brain injury.

Two double-blind, randomized, single-case experimental (baseline-amantadine-placebo-withdrawal) design (SCED) studies. Apathy measures included a Visual Analogue Scale (VAS), the Neuropsychiatric Inventory (NPI) apathy subscale and the Behavior Rating Inventory of Executive Function for Adults "Initiate" subscale. Safety measures included a rating scale of possible side effects of amantadine and physical examinations.

No difference in apathy symptoms (VAS) between baseline and amantadine phase was found in case 1 (NAP = 0.55). Surprisingly, in case 2, apathy symptoms deteriorated from baseline to amantadine phase (NAP = 0.28, 90% CI = −0.69 to −0.20) and improved from amantadine to placebo phase (NAP = 0.92, 90% CI = 0.60–1.00). This improvement was also found on the NPI apathy subscale. Side effects of amantadine were observed in case 2.

In this SCED study, amantadine did not improve apathy symptoms in two individuals with brain injury. However, this study shows that side effects of amantadine can occur which lead to a significant decrease in well-being. More high quality studies are required.

ARTICLE HISTORY
Received 2 October 2019
Accepted 12 October 2020

KEYWORDS
Brain injury; Amantadine; Apathy; Single-case experimental design

Acquired brain injury is a highly prevalent condition with functional impediment in physical, cognitive, emotional, behavioural and social domains

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Supplemental data for this article can be accessed https://doi.org/10.1080/09602011.2020.1842214

(Williams & Evans, 2003). Frontal lesions in particular often lead to behavioural problems (Eslinger & Geder, 2000), such as apathy, agitation and aggression, emotional lability and impairment of executive functioning.

The apathy syndrome is a frequent consequence of brain injury and is defined as a syndrome of primary motivational loss, that is, loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness (Marin, 1991). Furthermore, apathy includes a lack of purposeful behaviour, decrease of purposeful thinking and emotional indifference and affect flattening (Marin, 1991). The neurobiology of motivation and apathy is very complex. The frontal-subcortical circuitry and several neurotransmitter systems seem to be involved, amongst them dopamine and the N-Methyl-D-aspartate (NMDA) receptor (Marin, 1997).

Although prevalence estimates of apathy after brain injury vary widely depending on assessment tools and the clinical population studied (Le Heron et al., 2019), it is a common behavioural problem, with prevalence rates ranging from 20% to 71% in severe traumatic brain injury (TBI) (Stefan & Mathe, 2016) and from 15 to 72% in stroke (Caeiro et al., 2013).

Currently, no evidence-based treatment for apathy after brain injury is available, but pharmacological treatment may be considered as a treatment option. Amantadine is commonly used in clinical practice for treatment of apathy (Kant & Smith-Seemiller, 2002), has frequently been suggested as a treatment for apathy after brain injury (Arciniegas et al., 2000; Kant & Smith-Seemiller, 2002; Marin et al., 1995), and clinical experience suggests that it is safe. Amantadine has originally been developed as an antiviral agent. Later, it was discovered by chance that it was useful for treating Parkinson's disease and counteracting secondary neuroleptic symptoms. Despite the fact that the mechanism of action of amantadine is not fully understood, it is believed that clinical effects of amantadine are mediated through its antagonism at the NMDA subtype of glutamate receptors and its dopamine agonism (stimulating dopamine release and increasing dopamine availability) (Aoki & Sitar, 1988; Kraus et al., 2005).

Although amantadine has frequently been suggested as a treatment for apathy after brain injury, scientific studies on the efficacy of amantadine as a treatment for apathy after brain injury are scarce and of low methodological quality (Arciniegas et al., 2004; Kraus & Maki, 1997; Ter Mors et al., 2019; Van Reekum et al., 1995). In order to guide clinical decision making about pharmacological treatment for apathy after brain injury, more studies, particularly higher quality studies, are necessary.

Therefore, the main aim of the current study was to examine the efficacy of amantadine on apathy, due to frontal lobe brain injury or to injury of the efferent and/or afferent pathways of the frontal lobes, and to examine the safety of amantadine using single-case experimental design (SCED) in two patients. SCED is considered to be methodologically strong and is frequently used in brain injury populations because of the heterogeneity of this population

(Perdices & Tate, 2009). Our main research questions were: (1) Does amantadine lead to a decrease (improvement) in apathy symptoms? (2) Does amantadine administration lead to side effects?

Materials and methods

Design

The current study is part of a larger series of SCED studies examining the effect of amantadine on several target behaviours in individuals with brain injury. The current study is focused on apathy and consisted of two SCED's: two double-blind, randomized, placebo-controlled ABA withdrawal designs. Each SCED had an A-A1-B-A, or A-B-A1-A design (A = baseline/withdrawal; A1 = placebo; B = amantadine) (Table 1). The order of the experimental phases (A1-B or B-A1) was randomized. The pharmacist was in charge of randomization.

Blinding

To ensure blinding of procedure, the participant, significant other or the responsible nurse-for-the-day (depending on whether the patient was in -or outpatient), the nurse practitioner and the research team were blind to the treatment condition. The participant, significant other, and the nurse were not aware of the switch between the placebo and amantadine phase after five weeks. Furthermore, everyone was blinded to the assignment of treatment condition until analyses were performed.

Participants

The study was conducted at the Multidisciplinary Specialist Center for Brain Injury and Neuropsychiatry of Huize Padua, GGZ Oost-Brabant, a specialized

Table 1. Two possible dosage schedules for administration of amantadine and placebo

Schedule 1						
Time of administration	A (baseline)	A1 (placebo)	B (amantadine)			A (withdrawal)
	± 2 weeks	5 weeks	Day 1-7 1 week	Day 8-28 3 weeks	Day 29-35 1 week	± 4 weeks
8.00 AM	No pills	Placebo	100mg	100mg	100mg	No pills
12.00 PM	No pills	Placebo	Placebo	100mg	Placebo	No pills

Schedule 2						
Time of administration	A (baseline)	B (amantadine)			A1 (placebo)	A (withdrawal)
	± 2 weeks	Day 1-7 1 week	Day 8-28 3 weeks	Day 29-35 1 week	5 weeks	± 4 weeks
8.00 AM	No pills	100mg	100mg	100mg	Placebo	No pills
12.00 PM	No pills	Placebo	100mg	Placebo	Placebo	No pills

Note: the dosage of amantadine was increased gradually from 100mg (including 1 placebo pill and 1 amantadine pill of 100mg) in the first week to 200mg (2 times 1 amantadine pill of 100mg) in the second, third and fourth week of the amantadine phase. In the last week the dosage of amantadine was decreased again to 100mg (1 placebo pill and 1 amantadine pill of 100 mg).

mental health care institution in Boekel, The Netherlands. Potential participants were recruited on the basis of consecutive case finding from the outpatient brain injury clinic and from the inpatient brain injury rehabilitation facility. The present study describes participants included during the period of 12-08-2015–14-09-2016. Subjects with acquired brain injury to the frontal lobes or its afferent and efferent pathways, due to various aetiologies (stroke, TBI, brain infections, tumours, hypoxia) as verified by CT or MRI, suffering from apathy (established through clinical observation) and receiving care at the brain injury department of Huize Padua were eligible for participation. Other inclusion criteria comprised age (18 years or older) and time since injury (longer than 3 months). Subjects had to give written informed consent before participation. When there was incompetence to understand the information provided and informed consent of the patient was not possible, his/her lawful representative had to give informed consent in accordance with the Dutch law on the medical treatment contract (WGBO). Exclusion criteria were: current drug addiction, current psychosis, suicidality, current use of medications incompatible with amantadine (methylphenidate, typical or atypical antipsychotics, combination diuretics [hydrochlorthiazide + potassium sparing diuretics] or Levodopa), hypersensitivity to amantadine or any of the excipients, pregnancy and lactation, kidney failure (eGFR<10 ml/min), heart failure, refractory epilepsy, history of gastric ulceration, and current glaucoma. Concomitant non-pharmacological interventions were not restricted. Other psychopharmacological interventions (other than amantadine and medications incompatible with amantadine) were allowed if on a stable dose for four weeks. Escape medication, lorazepam 1 mg tds max, was allowed for a fortnight max.

Measures

Demographic characteristics

Information on demographic characteristics (age, sex, marital status, level of education, brain injury characteristics) was derived from medical files or was asked by the principal investigator at baseline.

Outcome measures

Primary apathy outcome measure. The Visual Analogue Scale (VAS) served as a tailored primary outcome measure of apathy. The VAS consisted of a horizontal line ranging from 0 to 100 and was tailored to the specific target behaviour of each patient, determined by the principal investigator. The patient's significant other (in case of outpatient treatment) or the responsible nurse-for-the-day (in case of inpatient treatment) was asked to make a subjective estimate of the specific target behaviour looking back over the day by placing a mark on the line at the end of every day. For every data point, a VAS score was calculated ([centimetres/total line length]*100). The VAS is particularly suitable for the

assessment of subjective phenomena (Gift, 1989) and has been used previously to rate behaviour of paediatric brain injury patients (Nowicki et al., 2019), to rate behaviour in the elderly (Morrison, 1983), and to measure the severity of aggressive incidents on psychiatric wards (Nijman & Palmstierna, 2002). Furthermore, the scale has shown to have good inter-rater reliability, test-retest reliability and validity (Morrison, 1983).

Secondary apathy outcome measures. The Neuropsychiatric Inventory (NPI) (Cummings, 1997; Cummings et al., 1994) was used to examine apathy with a standardized instrument. The NPI is an interview with a caregiver (in this study significant other or nurse) and concerns behavioural problems of the participants in the past four weeks. The NPI assesses behavioural changes since injury and consists of twelve behavioural subscales (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities). Each domain can be scored a maximum of twelve points (frequency x severity) with a maximum total score ranging from 0 to 144. The higher the score, the more frequent or severe is the behaviour. In the current study, the score (frequency*severity) on the apathy domain (NPI-A) was used to measure apathy. See Appendix 1 for psychometric properties of the NPI.

The Dutch version of the Behaviour Rating Inventory of Executive Function for Adults (BRIEF-A) (informant version) was used to assess the frequency of problems in executive functioning (Roth et al., 2005; Scholte & Noens, 2011). The BRIEF comprises 75 items about the frequency of experienced problems on a specific task/activity in the previous month, rated on a 3-point scale by the caregiver. These questions are divided into nine clinical subscales, which are further divided into the "Behavioural Regulation index" and the "Metacognition Index." Outcome scores are T-scores for every domain, both indexes and for the total score. A T-score of $\geq$65 is considered aberrant and is used as a threshold for clinical significance of reported problems (Scholte & Noens, 2011). In the present study, the score on the clinical subscale that best fit the target behaviour of each participant was used, in this case the "Initiate" subscale. See Appendix 1 for psychometric properties of the BRIEF-A.

Control measures. Control measurements were performed to control for changes in behaviour (other than apathy) and cognitive functioning, which might be due to external factors (e.g., neurodegeneration or development of (new) psychiatric problems) and might influence the effect of amantadine on apathy. Control measures of behaviour were the total score on the NPI (total mark-up of neuropsychiatric symptoms) and scores on both indexes of the BRIEF-A. Scores on these measures, except for the score on the apathy domains (NPI-A or BRIEF-Initiate), were not expected to change. In addition,

the DSM-IV-TR (Diagnostic and Statistical Manual-IV-Text Revision) classification (American Psychiatric Association, 2000), the classification used in the Dutch registration system at the time of the experiment, including the Global Assessment of Functioning score (GAF), which is a measure of psychological, social and occupational functioning and indicates the severity of illness on a scale from 0 to 100, was established by the principal investigator by performing a clinical interview (no change was expected). Last, the Mini Mental State Exam (MMSE) (Folstein et al., 1975) was used to control for changes in cognitive functioning. The maximum score of the MMSE is 30 (scores <24 indicate cognitive impairment).

Safety measures. A list of 37 of the most common side effects of amantadine (see Appendix 2) was created and administered by the nurse practitioner to monitor possible side effects of amantadine. Every participant had to rate the severity of the symptoms weekly on a 4-point scale (0 = absent, 1 = light, 2 = moderate, 3 = severe), leading to a maximum total severity score of 111. This score was used to display the course of complaints over phases and was interpreted qualitatively.

A weekly electrocardiogram (ECG) was performed by the nurse practitioner in order to detect emerging cardiac problems. In case of ECG alterations a cardiologist would have been consulted. In addition, heart rate measurements and blood pressure measurements (standing up and lying down) were performed.

Intervention

Amantadine hydrochloride and a visually identical placebo (microcrystalline cellulose) were administered during the intervention phase. Amantadine is absorbed slowly but almost completely. Peak plasma concentrations of approximately 250 and 500 ng/ml are seen three to four hours after single oral administration of 100 and 200 mg amantadine, respectively. In order to gradually introduce and withdraw amantadine, 100 mg amantadine was administered in the first and last week of the amantadine phase and 200 mg in the second to fourth week. Three weeks of 200 mg was considered enough time because following repeated administration of 200 mg amantadine daily the steady-state plasma concentration settles at 300 ng/ml within 3 days (Aoki et al., 1985; Aoki & Sitar, 1988; Gualtieri et al., 1989). Regarding the wash-out period, amantadine is eliminated in healthy young adults with a mean plasma elimination half-life of 15 h (www.accessdata.fda.gov). Participants were provided with a container for every week. To ensure optimal efficacy of amantadine, medication compliance must be >80% (Tate et al., 2013). In this study, treatment adherence was checked by the principal investigator by asking the participant and caregiver about the pill intake.

Procedure

This study was approved by the medical-ethics committee of the MUMC (Medisch Ethische Toetsings Commisie) (METC) and the internal ethical board of GGZ Oost-Brabant. The study was registered with the EudraCt number 2012-005723-33. Eligible participants were provided with information about the study verbally and in writing by the principal investigator and after one week the principal investigator saw the patients with their significant other in an interview to provide detailed information about the experiment. After the interview, the patients were offered two weeks time to consider their involvement and thereafter, the informed consent form was signed by the patient. After informed consent was obtained and prior to starting the baseline measurements, the physician assistant performed safety measurements (ECG, blood pressure, heart rate). Depending on the medical history of the subject the necessity of a cardiologic or neurological consultation was determined. When all inclusion criteria were met and no exclusion criteria emerged, baseline measures were performed by the principal investigator. Table 2 provides an overview of the measurement schedule. The study design accounted for the pharmacodynamics of amantadine as the measurements of the secondary outcome measures took place in the third week (17th day) of the amantadine phase (during the steady state of 200 mg), in the third week (17th day) of the placebo phase (plasma levels of amantadine are eliminated) and in the fifth week (day 31) of the withdrawal phase (plasma levels of amantadine are eliminated).

Analyses

Visual analysis

Data on the primary outcome measure (VAS apathy) were plotted in a line graph and were evaluated using visual analyses based on the features of visual analysis

Table 2. Overview of measures.

Measures	Measurement occasion	Measurement Performed by
VAS apathy	Daily	Partner or nurse-for-the-day
NPI, BRIEF-A, MMSE	Once per phase (baseline, amantadine, placebo and withdrawal)*	Principal investigator
DSM-IV-TR	At baseline and during withdrawal	Principal investigator
ECG and blood pressure	Weekly	Nurse practitioner
Side effects questionnaire	Weekly	Nurse practitioner

Abbreviations: VAS, Visual Analogue Scale; NPI, Neuropsychiatric Inventory; BRIEF-A, Behaviour Rating Inventory of Executive Function for Adults; MMSE, Mini Mental State Examination; DSM-IV-TR, Diagnostic and Statistical Manual-IV-Text Revision; ECG, Electrocardiogram

*Measurements took place in the third week (17th day) of the amantadine and placebo phase and in the fifth week (day 31) of the withdrawal phase.

(Kratochwill et al., 2013): level (mean and median score per phase), trend (simple linear regression trend lines were superimposed on the graphed data using Excel and trend was quantified by the unstandardized regression coefficient), variability (range of scores and establishing an "stability envelope": the median VAS apathy score for the baseline phase +/- 25% of this median score was calculated to determine whether at least 80% of the data fell within the stability envelope and this envelope was used to determine variability in all phases (Lane & Gast, 2014)), overlap (in this study calculated with nonoverlap of all pairs [NAP](Parker & Vannest, 2009)), and consistency of data patterns across similar phases (in this study defined as the consistency between baseline and withdrawal phase).

The total severity of complaints was plotted in a line graph to allow for visual inspection.

Statistical analysis

For daily apathy VAS data and for the side effect scale data, we first checked whether the baseline trend was statistically significant. An online calculator was used to calculate Tau-U and to perform statistical analyses (Vannest et al., 2016). One advantage of Tau-U compared with other non-overlap techniques is that it can control for baseline trend. However, in the absence of a baseline trend, NAP (Parker & Vannest, 2009) tends to be a less complex and better interpretable statistical method. As no significant baseline trend was present in either of the cases, we decided to use NAP for further analysis. NAP is appropriate for nearly all data types and distributions and strengths of NAP are its simplicity and its reflection of visual nonoverlap (Vannest et al., 2016). NAP can be derived from a Mann-Whitney U test and is interpreted as the percentage of all pairwise comparisons across Phases A and B, which show improvement across phases or, more simply, "the percentage of data which improve across phases." It is calculated as the number of improving or positive (Pos) pairs plus half of ties (.5 × Ties), divided by all pairs (Pairs): NAP = ([Pos + .5 × Ties] / Pairs) (Parker et al., 2011). NAP scores range from 0.50 to 1.00 for nondeteriorating (or increased) performance and below 0.5 for deteriorating (or decreased) performance during the intervention phase (Parker & Vannest, 2009). NAP values can be interpreted as treatment effects and can be classified as: weak effects: 0–0.65; medium effects: 0.66–0.92; large or strong effects: 0.93–1.0. (Parker & Vannest, 2009). To calculate NAP, an online calculator was used (Vannest et al., 2016). Alpha was set at 0.05. In the current study, for some contrasts of phases a decrease in behaviour (instead of increase) was considered favourable. By default, NAP output derived from the online calculator represents the percentage of improvement in behaviour, thereby expecting scores to increase from baseline to intervention phase. When a decrease in behaviour or symptoms was regarded as improvement in the current study, NAP was calculated as the number of negative (Neg) pairs plus half of ties (.5 × Ties), divided by all

pairs (Pairs): NAP = ([Neg + .5 × Ties] / Pairs). We calculated this by reversing the NAP that was derived from the online calculator (i.e., 1-NAP derived from output). The use of *p*-values for NAP requires the assumption of independent data (Pustejovsky & Swan, 2018) and the basis of the *p*-values for NAP has not clearly been explained in the presence of autocorrelation (Manolov et al., 2016), although in most cases the impact of serial dependence on effect sizes seems to be minor (Parker, 2006; Parker & Vannest, 2009). As autocorrelation is a common feature of SCED data, the *p*-values provided by the NAP analysis should be interpreted with some caution.

The Reliable Change Index (RCI) (Jacobson & Truax, 1991) was computed for the NPI frequency and severity apathy scores and was used to judge whether a possible change in scores can be attributed to genuine improvement in functioning rather than measurement error. Validation data of Cummings et al. (1994) were used for calculation of the RCI (see Appendix 3, Supplemental Table 1 for validation data and data used for calculation of the RCI). Outcomes are z-scores and therefore statistically significant when $z < -1.96$ or $z > 1.96$, based on a two-tailed effect. Because there was not enough psychometric data available to calculate the RCI, a decrease in T-score of the BRIEF-A subscale "Initiate" from above or at 65 (clinically significant (Scholte & Noens, 2011)) to below 65 was regarded as indicative of clinically relevant change.

Additional analyses

Change in control measures (NPI total score, MMSE score and DSM-IV-TR including GAF score) were examined by checking total scores, except for the BRIEF-A indexes for which T-scores were inspected to decide whether a change was clinically relevant.

Results

Case descriptions

Case description can be found in Box 1 and 2**.**

Box 1.

Case description Case 1

Case 1 was a 44-year-old man without a psychiatric history who was diagnosed in 2013 with a probable colloid cyst of the third ventricle. In 2014, a third ventriculostomy took place and ever since, there were problems with initiating behaviour. An MRI scan showed damage on the right side of the hypothalamus, where one of the two drains was placed, and at the bottom of the third ventricle, as a consequence of the ventriculostomy. The scan also showed that the colloid cyst was not removed completely. A PET scan showed subtle hypometabolism, especially at frontal and parietal regions of both sides of the brain. Case 1 was married and had received secondary vocational education. He worked in accountancy and was fully disabled due to the impairments following his brain injury. Cognitive impairments included problems with working memory, verbal memory, concentration and mental flexibility, as established by a neuropsychological examination in 2014. There were no motor impairments. At baseline, he used Pregabalin (Lyrica) 150 mg and Duloxetine (Cymbalta) 30 mg and he continued using this medication during the study without changes in dosage.

He was referred to our outpatient clinic because of apathy symptoms in June 2015. His target behaviour was described as "the amount of external prompting needed to initiate behavior." His partner rated this behaviour daily on a scale ranging from 0 to 100 (for this case, no horizontal line was used, but the partner had to write down a score) where a score of 0 indicated no external prompting needed to initiate behaviour and a score of 100 indicated that he constantly needed external prompting (i.e., without external prompting he does not initiate any behaviour). In agreement with the partner, it was decided that a score of 70 indicated that external prompting to initiate behaviour by the partner was needed approximately every $^{1}/_{2}$–$1^{1}/_{2}$ h for that day. According to the partner the apathy symptoms were independent of the kind of behaviour/activity. The time window for this measurements was from awakening in the morning till bedtime and this was fairly constant over the weeks of the experiment.

Measurements for case 1 took place from 12-08-2015 till 10-02-2016.

Box 2.

Case description Case 2.

Case 2 was a 64-year-old man with no psychiatric history, who suffered a cerebellar stroke when he was 60 years old. He recovered well during rehabilitation. At 61, he suffered a transient ischaemic attack, and at 62 years old, he suffered a recurrent cerebellar stroke from which he did not recover well, despite of an outpatient rehabilitation programme. An MRI showed cerebellar ischemia on both sides, alongside posterior white matter lesions, and a left-sided parietal ischemia, possibly of recent origin. Ever since the most recent stroke, he experienced a loss of motor skills, had trouble concentrating and showed hypersensitivity to noise. Furthermore, he showed symptoms of apathy. Case 2 was married and had received lower vocational level. He was retired at the time of the injury. Before retirement he worked as a postman. He suffered from cognitive problems, including memory problems and poor concentration, and he was hypersensitive to noise. These problems were based on anamnestic information (no neuropsychological examination was performed). In addition, case 2 had impairments in the fine motor skills. He used medication for prevention of recurrent strokes, but no other (psychotropic) medication and there were no changes in medication or dosages during the study. He received occupational therapy sessions weekly at home during the current study.

Case 2 was referred to our outpatient clinic in March 2016, because of persistent lack of initiative. According to his partner, he was inactive, sat on the couch all day and waited for her to give him directions. The target behaviour was described as "the amount of self-initiated activity per day." His partner rated this behaviour on a scale ranging from 0 to 100 at the end of each day. Every form of self-initiated activity (in and outdoors) resulted in a VAS score >0. A score of 100 reflected maximum possible amount of self-initiated activity defined as all activities of daily living that were self-initiated. The time window for this measurements was from awakening in the morning till bedtime and this was fairly constant over the weeks of the experiment.

Measurements for case 2 took place from 11-05-2016 till 14-09-2016.

Case 1

Case 1 was randomly assigned to Schedule 2 (Table 1).

Treatment adherence

All pills were taken during medication phase (amantadine and placebo) according to case 1 and his partner.

Primary apathy outcome measure

The baseline phase was extended due to delivery problems of the capsules. Table 3 shows the descriptive data of the visual analyses and Figure 1 shows apathy scores per day for case 1. Scores showed little variability within phases (>80% of the data points fell within the stability envelope) (Table 3, Figure 1). In both the amantadine phase (regression coefficient = −0.20) and placebo phase (regression coefficient = −0.18) there was a decelerating trend (decrease in apathy symptoms). There was a minimal/no trend in the baseline phase (regression coefficient = 0.02) and

Table 3. Descriptive data of visual analyses on the daily apathy measure (case 1).

	Number of measurements	Mean*	Median*	Range	Percent on or in stability envelope
Baseline phase	62	70.2	70.0	60.0–80.0	98.4%
Amantadine phase	35	69.1	70.0	50.0–90.0	82.5%
Placebo Phase	35	61.7	60.0	50.0–90.0	97.1%
Withdrawal phase	31	70.0	70.0	70.0–70.0	100.0%

*Higher scores indicate that the participant needed more external control to initiate behaviour and therefore reflect more apathy symptoms.

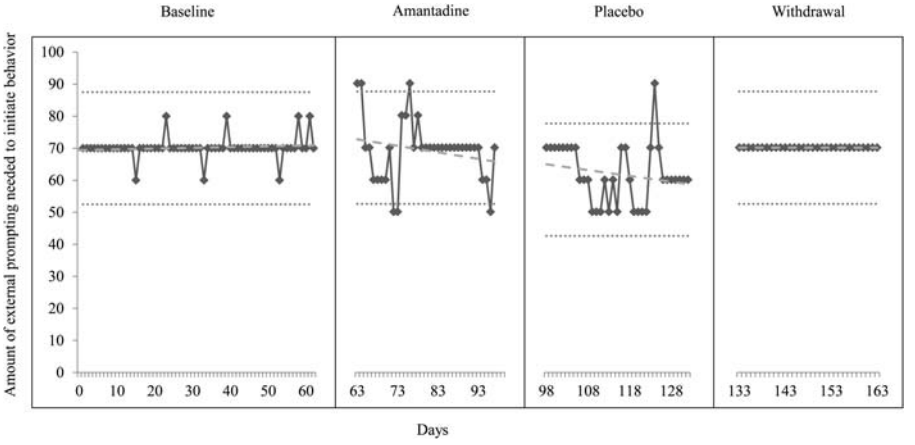

Figure 1. Apathy scores per day in separate phases (case 1).

Note: Dark grey solid lines represent daily apathy scores, light grey striped lines represent trend lines within each phase, and light grey dotted lines indicate the stability envelope. Higher scores indicate that case 1 needed more external prompting to initiate behaviour and therefore reflect more apathetic behaviour (a score of 0 = no external prompting needed, 100 = individual needs external prompting constantly to initiate behaviour, i.e., he does not initiate any behaviour). Highest dosage of amantadine (200 mg) is administered from day 70 till day 90.

withdrawal phase (regression coefficient = 0). There was consistency in scores across the baseline and withdrawal phase (in both phases minimal to no variability, minimal/no trend, and identical median scores).

There was practically no change in apathy behaviour from baseline to the amantadine phase (NAP = 0.55, 90% CI = −0.29–0.11). There was a medium improvement in apathy behaviour (decrease in the amount of external prompting needed to initiate behaviour) from amantadine to placebo phase (NAP = 0.71, 90% CI = −0.65 to −0.20). There was a deterioration in apathy behaviour (increase in apathy behaviour) from placebo to withdrawal phase (NAP = 0.20, 90% CI = 0.36–0.84).

Secondary apathy outcome measures

Due to the prolonged baseline phase, the NPI and BRIEF-A were administered twice. Scores were equal in the baseline (two measurements), amantadine, and withdrawal phase (NPI-A = 8). The NPI-A score was lowest in the placebo

phase (NPI-A = 6). There were no statistically significant differences in NPI-A frequency scores between the phases (RCI baseline vs. amantadine phase = 0; RCI amantadine vs. placebo phase= −0.89; RCI placebo phase vs. withdrawal phase = 0.89) and no statistically significant differences in NPI-A severity score (all RCI scores were 0) (Appendix 3, Supplemental Table 2).

T-scores on the "Initiate" domain of the BRIEF-A on the two baseline measurements were similar (77 and 80) and above threshold for clinically significant problems. Scores remained high and above threshold during the other phases (T-score amantadine phase = 71, T-score placebo phase = 68, T-score withdrawal phase = 74).

Control measures

Total NPI scores were similar for the different phases (baseline = 15 and 22, amantadine phase = 18, placebo phase = 19, withdrawal phase = 16).

The T-score on the Metacognition Index of the BRIEF (of which the "Initiate" domain is a subdomain) was above threshold at baseline (74 and 78). Scores remained high and above threshold during the other phases (amantadine phase = 70, placebo phase = 70, withdrawal phase = 76). T-scores on the Behaviour Regulation index were below threshold during all phases (baseline = 49 and 49, amantadine phase = 45, placebo phase = 49, withdrawal phase = 47).

DSM IV-TR diagnosis at baseline was Personality change after benign neoplasms in the brain, apathetic type 310.1, Cognitive disorder NOS 249.9. The baseline GAF score was 50, indicating serious symptoms or any serious impairment in functioning. This classification (including the GAF score) remained the same at the follow-up measurement.

MMSE scores for the different phases were 27 (baseline), 28, (baseline), 30 (amantadine phase), 29 (placebo phase), and 29 (withdrawal phase), indicating no substantial changes in cognitive functioning. The slight increase in score may be attributed to a learning effect.

Safety measures

ECG, blood pressure and heart rate measures showed no adverse effects of amantadine. Figure 2 shows the total severity score of complaints. The total severity score increased somewhat from baseline to the amantadine (this comparison is made with caution, because only 1 measurement was performed during baseline), increased slightly from the amantadine phase (median = 19.0) to the placebo phase (median = 21.0), and decreased from the placebo to the withdrawal phase (median = 12.0). Complaints rated moderate/severe during the amantadine phase only were: nervousness (week 4), depressed mood (week 4), and visual problems (week 7). The highest dosage of amantadine (200 mg) was administered from week 4 until week 6 (median = 19.0). During week 6 there was one missing value (for oedema). As this adverse effect was absent during all weeks of the study, the value was replaced by "0."

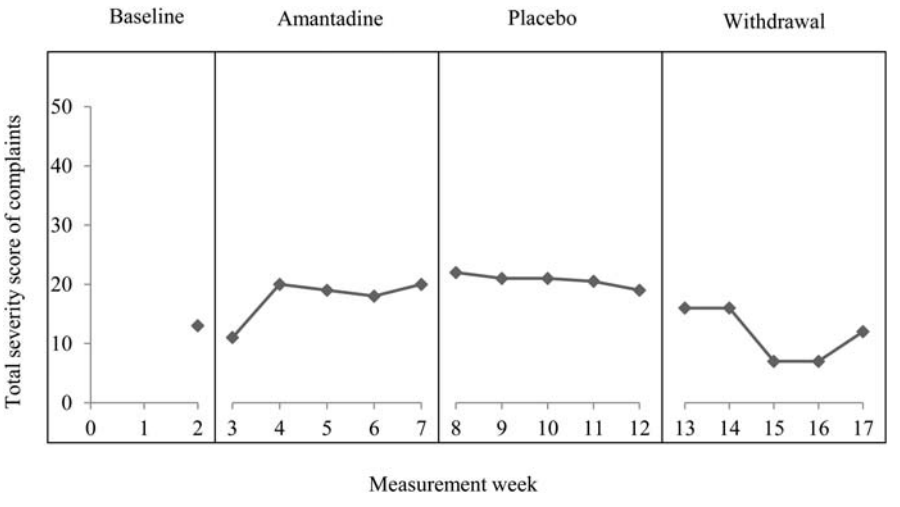

Figure 2. Severity of possible side effects (complaints) in separate phases (case 1).

Note: Total severity score is the sum of the severity scores for each complaint (0 = absent, 1 = light, 2 = moderate, 3 = severe), with a minimum score of 0 and a maximum score of 111. Dosage of medication during amantadine phase: week 3: 100 mg, week 4: 200 mg, week 5: 200 mg, week 6: 200 mg, week 7: 100 mg. In week 6 the score for one complaint was missing and was replaced by "0" (the score on the other measurements in that phase).

There was an increase in the total severity score (detoriation) from the amantadine to the placebo phase (NAP = 0.10, 90% CI = 0.17–1.00) and a decrease (improvement) from the placebo phase to withdrawal phase (NAP = 1.00, 90% CI = −1.00 to −0.37).

Case 2

Case 2 was randomly assigned to Schedule 2 (Table 1).

Treatment adherence

All pills were taken during medication phase according to case 2 and his partner.

Primary apathy outcome measure

Table 4 shows the descriptive data of the visual analyses and Figure 3 shows apathy scores per day for case 2. Scores ranged from 1 to 11, impeding visual

Table 4. Descriptive data of visual analyses on the daily apathy measure (case 2).

	Number of measurements	Mean *	Median *	Range	Percent on or within stability envelope
Baseline phase	26	3.1	2.7	2.0–7.3	84.6%
Amantadine phase	35	2.3	2.0	2.0–3.3	94.3%
Placebo Phase	35	6.6	8.0	1.3–10.7	54.3%
Withdrawal phase	23	5.3	6.0	3.3–6.7	69.6%

*Higher scores indicate a higher amount of self-initiated behaviour and therefore reflect less apathy symptoms.

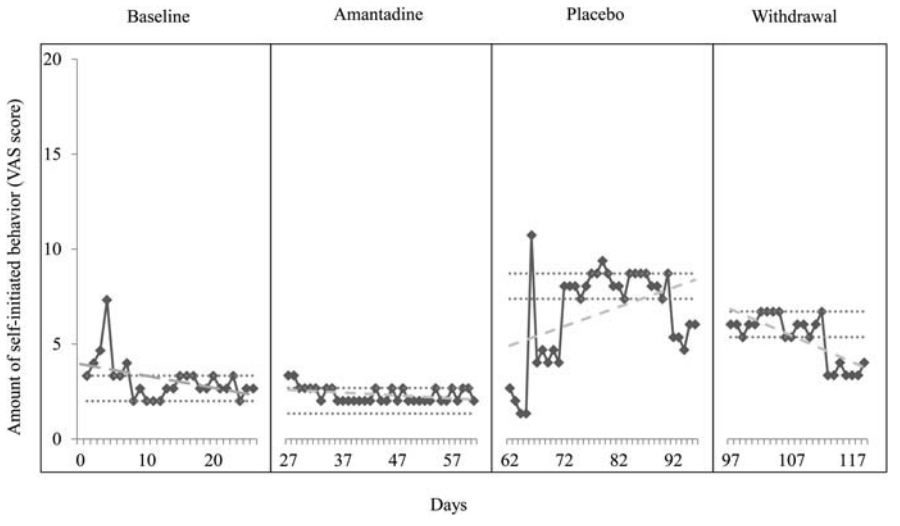

Figure 3. Apathy scores per day in separate phases (case 2).

Note: Dark grey solid lines represent daily apathy scores, light grey striped lines represent trend lines within each phase, and light grey dotted lines indicate the stability envelope. Higher scores indicate a higher amount of self-initiated activity and therefore less apathetic behaviour (a VAS score of 0 = no self-initiated activity, 100 = maximum possible amount of self-initiated activity during the day). Highest dosage of amantadine (200 mg) is administered from day 34 till day 54.

analysis on a 0–100 scale. Therefore, the range of the y-axis of the figure was set at 0–20. Visual analyses showed that scores in the baseline and amantadine phase showed little variability (>80% of the data points fell within the stability envelope). Scores in the placebo and withdrawal phase showed more variability (less than 80% of the data points fell within the stability envelope) (Table 4, Figure 3). There was practically no trend in the baseline phase (regression coefficient = −0.06) and amantadine phase (regression coefficient = −0.01). In the placebo phase there was an accelerating trend (an increase in self-initiated activity and therefore a decrease in apathy symptoms) (regression coefficient = 0.10) and there was a decelerating trend (a decrease in self-initiated activity and therefore an increase in apathy symptoms) in the withdrawal phase (regression coefficient = −0.14). There was no consistency in apathy scores across the baseline and withdrawal phase (more variability in the withdrawal phase, higher median score in withdrawal phase and a decelerating trend in the withdrawal phase compared with a minimal trend in the baseline phase).

With regard to the data, round numbers were used for NAP analyses (as we were not interested in score changes in decimals). From baseline to amantadine phase apathy behaviour deteriorated (the amount of self-initiated activity decreased) (NAP = 0.28, 90% CI = −0.69 to −0.20). From amantadine to placebo phase there was a large improvement in apathy behaviour (NAP = 0.92, 90% CI = 0.60–1.00) and from placebo to withdrawal phase there was a deterioration in apathy behaviour (NAP = 0.29, 90% CI = −0.67 to −0.16).

Inspection of data showed one potential outlier (on day 66, score=11). Removal of this outlier did not change results substantially.

Secondary apathy outcome measures

The highest NPI-A score was found in the baseline and amantadine phase (both NPI-A scores = 8). The score decreased to zero in the placebo phase and increased in the withdrawal phase (NPI-A score = 4). NPI-A frequency and severity scores were statistically significantly lower in the placebo phase compared with the amantadine phase (Appendix 3, Supplemental Table 3; RCI frequency score amantadine vs. placebo phase = −3.58; RCI severity score amantadine vs. placebo phase = −3.01). Severity scores were also statistically significantly higher in the withdrawal phase compared with the placebo phase (RCI placebo phase vs. withdrawal phase = 3.01). There were no other statistically significant differences in either NPI-A frequency scores (RCI baseline vs. amantadine phase = 0, RCI placebo vs. withdrawal phase = 1.79) or NPI-A severity scores (RCI baseline vs. amantadine phase = 0).

Regarding outcome scores on the "Initiate" domain of the BRIEF-A, data for one item were missing during placebo phase. According to the manual of the BRIEF-A, missing values should be replaced by a score of "1." However, we decided to replace the missing value by the score "2," which is the score that was most often given for the other items within this domain (on 6 of the 7 items) during the placebo phase and which is therefore more representative of the scores within this domain.

Scores were above cut-off in the baseline phase (T-score = 74), increased in the amantadine phase (T-score = 80), decreased to a score at the cut-off in the placebo phase (T-score = 65) and increased again to above cut-off in the withdrawal phase (T-score = 74).

Control measures

Total NPI scores were highest in the amantadine phase (NPI total = 29). Scores in the other phases were lower (NPI-total baseline = 10, placebo phase = 8, withdrawal phase = 4). Further inspection of data showed that neuropsychiatric symptoms during baseline consisted of symptoms of depression, anxiety, and apathy. During amantadine phase, symptoms on several domains increased and consisted of depression, anxiety, sleep disturbances, and change in appetite (decrease in appetite and weight loss) besides complaints of apathy. The NPI Total score during the placebo phase consisted solely of a change in appetite (an increase in appetite and weight gain). During the withdrawal phase, the neuropsychiatric symptoms consisted of apathy symptoms again.

The T-score on the Metacognition Index of the BRIEF was above threshold at baseline (T-score = 70) and in the amantadine phase (T-score = 71). The score decreased to below threshold in the placebo phase (T-score = 61) and remained below threshold in the withdrawal phase (T-score = 63). The decrease in the

Metacognition index T-score from amantadine to placebo phase was mainly due to a decrease in scores (indicating a decrease in problems) on the following subscales: Initiate (T-score amantadine phase = 80, T-score placebo phase=65), Working memory (T-score amantadine phase = 72, T-score placebo phase=57) and Planning and organization (T-score amantadine phase = 72, T-score placebo phase = 62). T-scores on the Behaviour Regulation index were below threshold during all phases (baseline: T-score = 62, amantadine phase: T-score = 57, placebo phase: T-score = 59, withdrawal phase: T-score = 56).

DSM IV-TR diagnosis at baseline was Personality change after brain injury (CVA), apathetic type 310.1, Cognitive disorder NOS 294.9. The baseline GAF score was 50, indicating serious symptoms or any serious impairment in functioning. This classification (including the GAF score) remained the same at the follow-up measurement.

MMSE scores were similar across phases (baseline = 29, amantadine phase = 30, placebo phase = 30, withdrawal phase = 30).

Safety measures

The ECG, blood pressure and heart rate measures showed no adverse effects of amantadine. Figure 4 shows the total severity of complaints. The total severity score started off rather high and decreased during the baseline phase (baseline phase median = 12.0). The score increased slightly from baseline to amantadine phase (median = 14.0), with a peak during week 7, and decreased in the placebo phase (median = 3.0). The total severity score remained low in the withdrawal phase (median = 3.0). The following complaints were rated as moderately severe during the amantadine phase only: slurred speech (week 7, 8, 9),

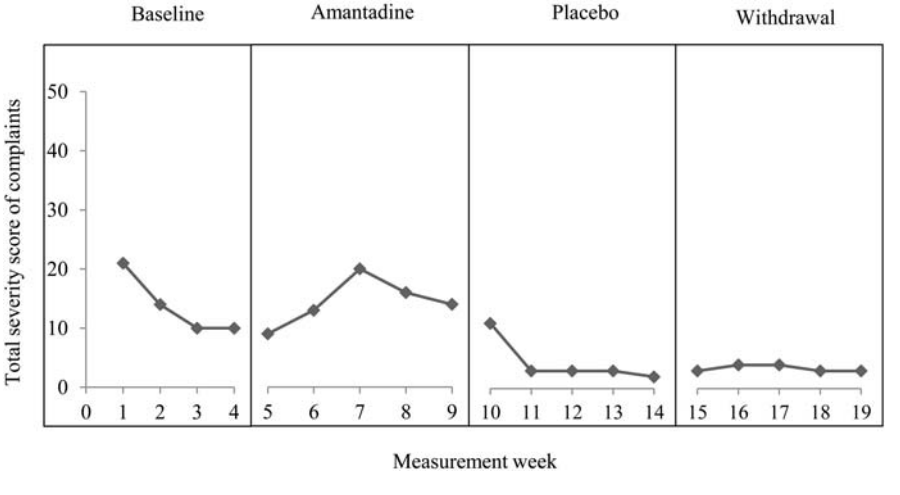

Figure 4. Severity of possible side effects (complaints) in separate phases (case 2).

Note: Total severity score is the sum of the severity scores for each complaint (0 = absent, 1 = light, 2 = moderate, 3 = severe), with a minimum score of 0 and a maximum score of 111. Dosage of medication during amantadine phase: week 5: 100 mg, week 6: 200 mg, week 7: 200 mg, week 8: 200 mg, week 9: 100 mg.

obstipation (week 7), loss of appetite (week 7, 8, 9), and urine retention (week 6, 7, 8). None of the complaints was rated as severe during the amantadine phase only. The highest dosage of amantadine (200 mg) was administered from week 6 till 8 (median severity score = 16). By week 6, case 2 had taken the highest dosage for only 3 days.

There was a large decrease in the severity score (improvement) from amantadine to placebo phase (NAP=0.96, 90% CI=−1.00 to −0.29). Comparisons between the other phases showed only small changes that were not statistically significant (baseline vs. amantadine phase: NAP=0.48, 90% CI= −0.62–0.72; placebo vs. withdrawal phase: NAP = 0.38, 90% CI=−0.39–0.87).

Discussion

The aim of the current study was to examine the efficacy and safety of amantadine for treatment of apathy in two cases with brain injury, by performing two SCEDs. Both SCEDs showed that amantadine did not improve apathy symptoms. Surprisingly, in both SCEDs we found that apathy symptoms (daily measures) improved in the placebo phase as compared with the amantadine phase, which preceded the placebo phase. This improvement was most pronounced in case 2. In addition, this improvement was also found on a secondary apathy outcome measure (NPI-Apathy) for case 2 (not for case 1).

In case 1 there were no indications of side effects of amantadine. However, in case 2, there were indications of side effects. Some complaints (slurred speech, loss of appetite and urine retention) were rated by case 2 as moderately severe during the amantadine phase only, particularly during the highest dosage of amantadine administration. Furthermore, the severity of complaints decreased remarkably when amantadine administration switched to placebo. In addition, the increase in neuropsychiatric symptoms (NPI-total score, control measure), as reported by the partner during the amantadine phase, also seems to reflect side effects of amantadine and a general feeling of discomfort in case 2.

The decrease in the severity of complaints (indicative of a relief of side effects) in the placebo phase may explain why apathy symptoms improved in the placebo phase, as case 2 was feeling (relatively) better during this phase as compared with the amantadine phase. The finding that the total scores on the control measures (NPI and Metacognition index of the BRIEF-A) decreased from the amantadine to the placebo phase (indicating a decrease in problems) and the observation that case 2 was convinced he was doing better due to amantadine administration (although he was receiving placebo pills and was informed about this after the experiment) may provide additional support for this hypothesis. Although this may explain why apathy symptoms improved in case 2, it does not explain why apathy symptoms also improved in case 1 in the placebo phase. A more robust design may have been able to address these apparent anomalies. Furthermore, it may be hypothesized that the

improvement in apathy symptoms in the placebo phase could be due to amantadine preceding the placebo phase. However, amantadine has a mean plasma elimination half-life of 15 h and in both cases the improvement in apathy symptoms was observed five to seven days after amantadine administration was ended, making an (delayed) effect of amantadine unlikely.

Some previous studies did find an effect of amantadine on apathy (Arciniegas et al., 2004; Kraus & Maki, 1997; Van Reekum et al., 1995). The study by Van Reekum et al. (1995), which is the study with the best methodological design published so far (double blind, randomized, placebo-controlled single-case study), showed that amantadine was effective in improving initiation and progress/participation in therapy in an individual with profound apathy following TBI. Detailed inspection of the results, however, shows that the improvement in apathy symptoms was small and that there were quite some differences in the scores between the therapists who scored the behavioural inventory. Furthermore, no visual or statistical analyses were performed and therefore it cannot be concluded if the found differences were beyond mere random fluctuations. Other previous studies were of lower methodological quality and only included descriptions of apathy symptoms (Arciniegas et al., 2004; Kraus & Maki, 1997). These studies showed some positive effects of amantadine on certain aspects of frontal lobe disorders, including loss of motivation (Kraus & Maki, 1997), and on cognitive and neurobehavioral problems, including apathy (Arciniegas et al., 2004). As these studies did not include experimental control conditions and did not use quantitative measures, effects could possibly be explained by other factors such as spontaneous recovery, observer bias or placebo effects, instead of being an effect of amantadine itself.

There are several possible explanations for the lack of an effect of amantadine in the current study. First, effects of amantadine may have been masked by the side effects that were reported by case 2. However, this does not explain the results of both cases, as there were no indications of side effects in case 1. Second, it may be hypothesized that amantadine improves apathy symptoms in brain injury patients with other characteristics (e.g., severity and type of injury, time since injury, severity of cognitive problems), than the patients included in our SCEDs, who both suffered from non-traumatic brain injury, were in the chronic phase after brain injury and suffered from several cognitive problems. Third, amantadine's mechanism of action is not fully understood and the efficacy of amantadine as a treatment for apathy after brain injury has only been supported by clinical experience and a few studies with low methodological quality and/or unconvincing results. Therefore, another explanation for the lack of an effect in the current study may be that amantadine actually does not improve apathy symptoms after brain injury. However, more high-quality studies are needed to confirm or disconfirm this.

Regarding the safety of amantadine, some previous case (series) studies examining the effect of amantadine on behavioural problems in patients with

brain injury showed indications of side effects of amantadine. Two out of seven cases in a case series study on apathy (Kraus & Maki, 1997) showed suspected side effects (light-headedness for which amantadine was discontinued, nausea, vomiting, hyperactivity, facial twitch, and abnormal thyroid results). In addition, in a case series study on aggression (Nickels et al., 1994), possible side effects were found in five (out of twelve) cases, including hypomania, pedal oedema, generalized seizures, and visual hallucinations. Other studies on amantadine and problem behaviour after brain injury showed no side effects (Arciniegas et al., 2004; Hammond et al., 2014; Hammond et al., 2017; Hammond et al., 2015; Van Reekum et al., 1995). So, results of previous studies seem to indicate that amandine is a safe drug, but that at least in some patients (as shown by case studies), side effects can occur for which discontinuation or dose reduction may be necessary, which is in line with the results of our study. It must, however, be noted that the previous case studies were of low quality (uncontrolled) and therefore it is possible that the found side effects were (also) due to factors other than amantadine (e.g., usage of other medication during the study or medical conditions).

The major strength of the current study is that it is the first randomized SCED study that includes both visual and statistical analyses to examine the efficacy of amantadine as treatment for apathy after brain injury. Furthermore, the daily apathy measurements yielded an abundant number of data points, enabling statistical analyses and reducing the possibility of finding an effect by chance rather than a real-life effect. In addition, the current study included an extensive monitoring of possible side effects of amantadine.

The current study also has some limitations. First, the design of our study does not provide three demonstrations of the treatment effect of amantadine which are needed to achieve sufficient internal validity (Tate et al., 2013). Our study design provides only one or two demonstrations of the treatment effect, depending on whether the second demonstration (amantadine vs. placebo) is considered as a treatment effect of amantadine. As placebo may be considered as an alternate treatment, one may argue whether the second demonstration is a demonstration of the treatment effect of amantadine or the effect of amantadine relative to the effect of another treatment (placebo). To achieve high internal validity, more extensive/robust designs could be used, like an A (B or C), A (B or C), A (B or C), A (B or C) design, where B stands for amantadine and C stands for placebo and where two occurrences of each phase are randomized across the four possible points in the sequence. Although such a design would be more internally valid, it also increases the chance of drop-out and participants have to be willing to switch from amantadine to placebo multiples times, which may become problematic when amantadine has a strong clinical effect or leads to side-effects.

Second, as only two SCEDs were performed, we cannot generalize our findings to all individuals with brain injury. In order to achieve good external

validity, three direct or systematic replications of the experiment are needed (Barlow et al., 2009; Tate et al., 2013), which means that two direct replications extra are needed, as case 2 in our study can be regarded as a replication of case 1. In addition, the two cases were different with respect to some characteristics including age, motor impairments, occupation, educational level, cognitive problems, and type of brain injury. The differences in response to amantadine between the two cases in the current study (although they were relatively modest) may reflect differences in (some of) these characteristics. Future studies with comparable cases are needed to confirm the results of the current study.

Third, the daily measures were not standardized measures. However, the standardized measures we did use showed similar results as the daily measures. In addition, although VAS measures have been shown to have a good inter-rater reliability (Morrison, 1983), we were not able to calculate the inter-rater reliability of our specific VAS measures, because only one person performed the measurements. Furthermore, we did not have a quantitative measure of treatment adherence and had to rely on the response of the participants and their partners.

Last, there are no agreed-upon criteria for statistical analyses for SCED data. In the current study we chose to use NAP because of its several advantages (appropriate for nearly all data types and distributions, its simplicity and its reflection of visual nonoverlap). We are aware that different techniques applied to the same data can yield different results (Brossart et al., 2006). As mentioned earlier, one disadvantage of NAP analyses is that it is not clear how its *p*-values are affected by autocorrelation, which is a common feature of SCED data, and which may lead to an elevated Type 1 error. However, we do not think this disadvantage was very problematic in the current study, since we did not find a statistically significant effect of amantadine (our main conclusion). Although auto-correlation may have impacted our findings that apathy symptoms statistically significantly improved from amantadine to placebo phase, these statistically significant changes were accompanied by medium to large effect sizes, which are only slightly influenced by serial dependence (Parker, 2006; Parker & Vannest, 2009).

Conclusions

In this SCED study, amantadine did not improve apathy symptoms in two individuals with brain injury. However, this study shows that side effects of amantadine can occur which lead to a significant decrease in well-being. At this point in time, evidence is too limited to draw firm conclusions about the efficacy and safety of amantadine in the treatment of apathy after brain injury. However, the outcomes of this study should at least lead to caution when considering the off-label use of amantadine for treatment of apathy.

More high quality (SCED) studies are required to make more conclusive statements on efficacy and safety.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix 1

Psychometric properties of the Neuropsychiatric Inventory and the Behavior Rating Inventory of Executive Function for Adults

Neuropsychiatric Inventory (NPI)

The NPI has a good overall internal consistency (Cronbach's α = .88) and sufficient test-retest reliability (r= 0.79 for frequency and r =0.86 for severity) (Cummings, 1997; Cummings et al., 1994). Because the study was conducted in the Netherlands, a Dutch version of the inventory was used (Jonghe de, Borkent, & Kat, 1997; Kat et al., 2002).

Behavior Rating Inventory of Executive Function for Adults (BRIEF-A)

The Dutch version of the informant questionnaire has good internal consistency for the total score (Cronbach's α = 0.97) and the behavioural regulation and metacognition indexes (Cronbach's α respectively 0.94 and 0.96). The test-retest reliability for the total score is sufficient (r = 0.78), with subscale test-retest reliability ranging from r = 0.66 to r = 0.88.

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Appendix 2

List of 37 possible side effects of amantadine. For each complaint the severity is scored (0 = absent, 1 = light, 2 = moderate, 3 = severe)

- Anxiety
- Headache
- Elevation of mood
- Lightheadedness
- Lethargy
- Hallucinations
- Nightmares
- Ataxia
- Slurred speech
- Blurred vision
- Loss of concentration
- Nervousness
- Depressed mood
- Insomnia
- Myalgia
- Confusion
- Disorientation
- Psychosis
- Convulsions

- Tremor
- Dyskinesia
- Visual problems
- Ankle edema
- Palpitations
- Orthostatic hypotension/posture dependent dizziness
- Shortness of breath
- Loss of appetite
- Diarrhea
- Obstipation
- Nausea
- Vomiting
- Dry mouth
- Diaphoresis
- Exanthema
- Photosensitization
- Urinary retention
- Urinary incontinence