Published in final edited form as:
Am J Phys Med Rehabil. 2007 August ; 86(8): 605–612.

Amantadine for adynamic speech: possible benefit for aphasia?

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Abstract

OBJECTIVE—Dopaminergic agents may stimulate behavior and verbal expression after frontal lobe dysfunction. Although amantadine is used in neurorehabilitation of motivational disorders and head injury, it is not commonly prescribed to improve aphasia. This pilot study examined verbal fluency on and off amantadine for nonfluent speech.

DESIGN—Four participants undergoing inpatient rehabilitation, meeting criteria for transcortical motor aphasia had stroke (2), stroke post-aneurysm surgery (1), or brain tumor resection (1). We administered amantadine 100 mg bid in an open-label, on-off protocol with multiple assessments per on-off period.

RESULTS—Off medication, subjects generated a mean 12.62 words (abnormally few) on the Controlled Oral Word Association test. On medication, word generation significantly improved to 17.71 words ($p = 0.04$), although scores remained psychometrically in the abnormal range.

CONCLUSIONS—Further research on amantadine specifically for nonfluent speech and nonfluent aphasia, including effect on functional communication and control conditions, may be warranted.

Keywords

amantadine; aphasia; rehabilitation

Hypothesis-driven physiological treatment of cognitive disorders, based upon cognitive neuropsychological models, could be considered true translational rehabilitation. Physiological treatment might be defined as somatic interventions to induce bodily changes directly, as contrasted with behavioral treatment consisting of controlling learning experiences in order to induce neurophysiological change indirectly. Unfortunately, a process of scientific translational method is still developing for physiological rehabilitation in the acquired speech and language disorder, aphasia.

Nonfluent aphasia occurs with post-stroke brain injury when subjects have 1) abnormal spontaneous speech and communication ability, with a conversation partner making the major portion of the effort supporting verbal communication and 2) nonfluent speech (fewer than 50 words per minute generated in response to an open-ended question such as “How did you come to the hospital?”). Even when subjects have relatively spared comprehension ability, the disability associated with nonfluent aphasia is considerable. Self-initiated verbal messages are a part of almost all daily life settings, and an impairment of spontaneous speech in nonfluent aphasia can significantly limit independence and psychosocial function (Herrmann and

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Financial disclosure: Dr. Barrett received funding and medication from UCB Pharma, Inc. in 2004 for an unrelated study of aphasia treatment. In connection with this work, Dr. Eslinger does not have any financial disclosures.

Wallesch, 1989). Other disorders primarily affecting attention (the ability to focus, remain vigilant, and ignore irrelevant stimuli) or conation (amotivational or apathetic states) may also produce a combination of communication disorder and nonfluent speech. We would suggest that although their problem is of different etiology, these patients are also significantly disabled.

Ideally, pharmacotherapy of aphasia might begin with an agent selected because its predicted mechanisms of action corresponds with specific dysfunctional processing in brain-behavior systems, or because an agent is known to act on neurotransmitter-neuroanatomic networks critical to a dysfunctional processes. However, the theoretical basis for improvement with some currently proposed agents for pharmacotherapy of aphasia is not specific to dysfunctional cognitive mechanisms. Instead, agents are often used that may benefit brain function more generally, e.g. decrease post-stroke diaschisis, induce a permissive state for plastic remodeling, or improve brain metabolic activity (Greener et al., 2001)

Both stimulants and dopamine agonists (e.g. bromocriptine) may stimulate behavior in brain-injured patients with frontal lobe syndromes (for a review, see DeMarchi et al., 2005). Dopamine agonists may also be helpful for aphasia (Raymer 2001). Amantadine, which has pro-dopaminergic and anticholinergic effects, has been in use for many years, has few side effects, is safe (Taus et al., 2003;Drayton et al., 2004) and inexpensive (Rothberg et al., 2003). Its primary indications in medicine, neurology and rehabilitation include as an antiviral (Rothberg et al., 2003), for fatigue accompanying chronic neurological disorders (Krupp et al., 1995), and to improve hyperkinetic and parkinsonian movement disorders (Anonymous, 2002). It is also widely used in neurologic rehabilitation for motivational disorders/minimally conscious state after traumatic brain injury (TBI; Meythaler et al., 2002;Whyte et al., 2002).

In contrast, it is not common rehabilitative practice to prescribe amantadine for communication disorders or nonfluent aphasia. In many rehabilitative settings, in fact, standard care of communication disorders in acute or chronic stages does not combine pharmacologic and behavioral treatment.

The magnitude of the problem of acute and chronic post-stroke aphasia mandates wider action to improve its disability (Sarno and Gainotti, 1998). There are an estimated one million stroke survivors with aphasia in the US alone (National Institute on Deafness and other Communication Disorders, 1997), thus a low-risk agent with even minor likelihood to benefit communication might have a significant impact on decreasing the individual and national burden of communication disorder, in lost work time for people with aphasia and their caregivers, dollars spent on care, and reduced quality of life.

Specific information about a possible effect of amantadine on nonfluent aphasia is not easily obtained. To locate recent studies on the use of amantadine in aphasia rehabilitation, we performed a Medline search of published literature 1966-present and Psychlit search of literature 1872-present using the terms “aphasia” “rehabilitation” and “amantadine, ” which identified no articles on either database. Searching “aphasia” and “amantadine” identified via Medline one Japanese language article on improvement of perseverative speech in three patients with 200 mg amantadine daily (Imamura et al., 1994). We then combined the search terms “amantadine” and “verbal behavior” to search both databases, but again no therapeutic articles were identified. Medline identified a case report of amantadine-induced vocal myoclonus (Pfeiffer, 1996).

We examined selected existing studies on the effects of amantadine on attention and cognitive function, to determine whether improvement in verbal fluency in patients meeting diagnostic criteria for aphasia was reported. Schneider et al. (1999) reported that amantadine 300 mg PO daily in traumatic brain injured patients, given in a placebo-controlled fashion to assess improvement in attention and higher cognitive skills, and reduction of agitation, did not have

significant effects. Naming and verbal fluency were examined in this negative study, but these two measures were collapsed into a composite cognitive variable and so medication effect is difficult to determine. In a case study reporting benefit of amantadine treatment in a patient with post-hypoxic encephalopathy and transcortical sensory aphasia, Arciniegas et al. (2004) included a summary statement that verbal fluency improved on amantadine, declined when it was tapered, and improved again when amantadine was reinstated. However, the patient's fluency and how it was evaluated were not specified. We were thus unable to find specific report of improved language output or verbal fluency with accompanying documentation.

One of us (AMB) previously attended on an acute inpatient neurological rehabilitation service. Established standard evaluation of patients with brain injury by the resident physician staff included assessing frontal lobe function and testing speech and language, including verbal fluency. A standard treatment administered to patients identified on screening as having frontal lobe dysfunction of the amotivational type, including isolated nonfluent speech, was amantadine 100 mg orally twice daily. In order to address the lack of specific reports of amantadine benefit in nonfluent aphasia, we retrospectively examined data collected on patients admitted for inpatient neurorehabilitation under AMB's care, in order to identify any patients meeting criteria for nonfluent aphasia who were treated with amantadine during July 1999-February 2001. On our unit, amantadine administered for the treatment of frontal lobe symptoms was given in a nonblinded protocol of multiple on-off sessions 2–6 days in length, in order to assist with determining, on an individual patient basis, whether to continue the medication at discharge. Our goal in examining this initial case series information collected on a clinical care unit, was to learn if there was evidence supporting further controlled research on amantadine in nonfluent aphasia.

Although amantadine has a longer half-life than do most clinically used stimulants, the clinical on-off regimen over multiple on-off cycles and multiple testing sessions used on the inpatient neurorehabilitation unit was based upon that used for administration of stimulants for attention-deficit disorder. We suggest that it may still be appropriate to the study of amantadine for treatment of aphasia. Based upon previous literature supporting the use of dopaminergic agents for nonfluent aphasia (Gold et al., 2000;Sabe et al., 1992), amantadine's cognitive effects on cognition can be postulated to be transient.

Subjects

We identified four records of consecutive patients admitted to the Neurological Rehabilitation Service at the Penn State Rehabilitation Center in the year 2000 (Mean 51.75 years of age, range 37–66 years; mean 10.75 years education, range 8–12 years) who met criteria for the diagnosis of nonfluent speech and were treated with amantadine for frontal lobe dysfunction of the amotivational type. To meet our clinical criteria for this diagnosis, subjects had to demonstrate: 1) abnormal spontaneous speech and communication ability, with the conversation partner making the major portion of the effort supporting verbal communication and 2) nonfluent spontaneous speech (fewer than 50 words per minute generated in response to an open-ended question such as "How did you come to the hospital?"). All subjects who were identified (see below) also exhibited 3) relatively spared comprehension of single words and simple commands, and 4) relatively spared repetition of single words and short phrases (e.g. "No ifs, ands or buts."), consistent with a possible diagnosis of transcortical motor aphasia.

In the acute rehabilitation hospital where the study was performed, clinical assessment with an instrument permitting aphasia subtyping was not standard. As the treating attending physician (AMB) felt that syndromic subtyping of speech and language disorders was necessary to plan theoretically-based treatment, resident physicians were trained to perform a bedside assessment of spontaneous speech, naming, comprehension, repetition, reading and

writing on every patient based upon Albert et al. (1981) and the Florida Mental Status Examination (Doty et al., 1990), repeated and confirmed in its essential parts by the attending physician. It should be noted that when the combination of nonfluent speech, relatively spared repetition and comprehension were noted on assessment, we did not rigorous distinguish whether nonfluent speech was primarily a result of language abnormality, or it was related to a primary attentional disturbance or abnormal conative function. It is possible that the subjects in this study suffered from the latter two disorders.

The subjects were all diagnosed as having a frontal lobe disorder of the primary amotivational type as part of a structured neurocognitive assessment carried out by the therapy and resident physician teams, confirmed in its essential parts by the attending physician (AMB) and based on the Florida Mental Status Exam (Doty et al., 1990). Amotivational frontal lobe dysfunction was defined as a disinclination to interact or behave which produced impairment on specific tasks and functional disability. Frontal lobe function was assessed by observing spontaneous interactive behaviors and speech, body kinesis, and activities of daily living. Our clinical criteria for the diagnosis of amotivational frontal lobe dysfunction required that subjects also have evidence of co-occurring motor response disinhibition, planning and organizational deficits, and/or deficits of abstract thinking. Although we cannot guarantee that speech therapy was completely identically administered, the same clinician treated all four patients in the study, and all patients were treated for one hour, five days weekly. This treatment situation was similar for occupational and physical therapy (although several OT/PT clinicians rotated depending on the day of treatment for these specialties). Subjects received treatment with amantadine for frontal lobe disorder as part of our inpatient rehabilitation unit's established clinical rehabilitation practice.

Method

Normal renal function as measured by screening blood urea nitrogen/creatinine was confirmed for all subjects before starting amantadine. We administered amantadine 100 mg PO bid (6 am and 6 pm) to all subjects in an on-off multiple-assessment protocol without blinding. Subjects received 1 day of amantadine 100 mg PO (6 am), with dosage increased to 100 mg PO bid thereafter, and were assessed between 2–6 days after starting amantadine. Patient 1 received four assessments, one per on-off session, with ABAB (off-on-off-on) design. Patients 2–4 received multiple assessments per off-on session, in an ABAB protocol for patients 2 (total 6 assessments) and 3 (8 assessments), and in an ABA (off-on-off) protocol for patient 4 (10 assessments), who was discharged before the last "on" session could be completed. "Off" periods commenced with one day during which subjects received a single dose of amantadine 100 mg PO (6 am). Mean 4.25 day drug washout periods were used (range 3–6 days).

We examined for evidence of possible treatment effect on verbal fluency by recording the results of bedside testing with the Controlled Oral Word Association Test (COWA) (Benton and Hamsher, 1989). Subjects were asked to generate words beginning with the letters F,A and S in one minute respectively, and score was the total number of allowable words generated (no derivatives, proper names, or repeated words were permitted). A priori, we hypothesized that performance on medication would improve compared with off-medication performance. Therefore, we compared mean performance on and off medication using a one-tailed, paired-sample Student's t-test.

An observed group effect may reflect improvement of similar magnitude in individual patients treated, or may sum disparate effects in different patients. Disparate treatment effects are of obvious clinical concern, as some patients may not benefit from a treatment or may even experience adverse effects. We anticipated that not enough trials per patient would be available to detect individual effects with sensitivity. However, to assess for robust disparate individual

effects in a preliminary fashion, we performed two-tailed, paired-sample t-tests for each subject, comparing mean performance on and off medication, with the understanding that a failure to obtain significance for these comparisons might be due to limited power.

Results

Amantadine is reported to be associated with the following side effects in more than 5% of people taking the medication: nausea, dizziness (lightheadedness) and insomnia. In 1-5% of patients, livedo reticularis, depression, irritability, hallucinations, confusion, anxiety, dry mouth, constipation, ataxia, peripheral edema, delirium, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue may occur (Mosby's Drug Consult, 2005,Silver and Sahs, 1972). The anticholinergic-like effects of amantadine may lead to delirium or attention/memory dysfunction. No side effects were reported in the patients studied during the time they took amantadine, or at any time during their hospitalization.

Off medication, participants generated a mean 12.62 words (Range 1.5–19.5) on the COWA (below the 1st percentile criterion for a hypothetical subject with 8 years education). On medication, group mean words generated increased (mean word generation 17.71 words, range 3.5–28 words; $t = 3.38$, $p = 0.043$, two-tailed). Results for each subject are presented in Table 1.

When results were examined individually with paired-samples, two-tailed t-tests, in only one subject (subject 1) did mean words generated on amantadine significantly exceed mean words generated off amantadine (see Table 1). However, all subjects generated more mean words on than they did off medication.

Discussion

The study was designed to examine preliminary data generated from clinical treatment of patients with frontal lobe syndromes with amantadine, to determine whether there appears to be feasibility for further study of the drug specifically as an agent for nonfluent aphasia. The participants in this retrospective analysis all had nonfluent speech and were diagnosed clinically as meeting criteria for diagnosis of transcortical motor aphasia (Type II, Benson and Ardila, 1996).

Among rehabilitation professionals, transcortical motor aphasia may not be regarded as the aphasia type most requiring treatment. However, impaired fluency, and impaired language production in general, may be a more relevant target for rehabilitation than other symptoms of aphasia (Mazzoni et al., 1992;Mazzoni et al., 1995). Fluency may be impaired because of grammatical or phonetic-articulatory deficit, as occurs in classical aphasia syndromes associated with left cortical injury. However, some patients are able to generate utterances that are from a grammatic and articulatory standpoint well-formed, but do not initate or elaborate verbal messages (Raymer, 2001). Although this may be an uncommon form of aphasia in people with left hemisphere ischemic injury, in our experience, it occurs commonly in neurological rehabilitation, and the underlying cause in neurorehabilitation patients may be diverse. Patients with nonfluent speech, but relatively spared comprehension and repetition, may have a primary disorder of language, or may primarily have impaired attention, or conation. These three disorders are supported by different brain-behavior systems and are impaired by theoretically distinct mechanisms. As in the current patient group, subjects with nonfluent speech may even demonstrate primary cortical pathology in the right hemisphere. In this setting, transcortical motor aphasia Type II might be a subset of adynamic frontal lobe disorders. Although these patients are not usually classified by their medical providers as

aphasic, they are almost invariably referred for, and receive, inpatient and outpatient speech therapy, acknowledging their need for improved communication ability. Appropriate medication treatment might augment communication recovery still further.

If transcortical motor aphasia, Type II is a subset of adynamic frontal lobe disorders, it may not be surprising that our retrospective examination of verbal fluency on and off amantadine suggested that amantadine is of potential benefit. In previous reports, adynamic behavior in frontal lobe disorders appeared to improve on amantadine (Patrick et al., 2003;Nickels et al., 1994). In other patient groups not specifically identified as having transcortical motor aphasia (Kraus and Maki, 1997), amantadine treatment was associated with improvement on the Controlled Oral Word Association task.

Although these findings are preliminary, we feel that they may be of pragmatic importance. Pharmacological treatments for aphasia are not yet standard in the assessment and care of aphasia. If amantadine, an inexpensive and safe drug that is easy to administer, improves verbal output even in only a subset of people with communication disorders, it may decrease cost of care, improve functional outcomes, and positively affect patients' and families' lives. Although it is possible that only subjects with adynamic transcortical motor aphasia may benefit from amantadine treatment, this c could be formally investigated in studies including subjects with other acute or chronic nonfluent aphasia syndromes.

Our study has significant limitations: although verbal fluency improved on amantadine, fluency was still uniformly below the normal range. Although it is possible that incremental improvement in fluency improved function, we do not have any evidence that occurred. Unfortunately, we did not specifically assess whether spontaneous word generation to an open question, or effort of communication, improved, and these also would be expected to improve communicative function. We do not have co-measured motor function to examine whether a general improvement in kinesis may underlie improved speech in our small group of subjects. The length of treatment needed for optimal results, additional functional and neuropsychological measures to be used to assess improvement, and timing of amantadine administration all need to be elucidated if the agent is to be recommended for clinical use, and a larger, prospective patient study may help to address these issues. This retrospective chart review study included data collected in a clinical, rather than a research setting. As a result, treatment criteria for prescription of amantadine may not have been as rigorously defined as would be appropriate in a research setting. Also, subjects included may have had different clinical characteristics and may have been more variable from each other than would be expected in prospective clinical research--some patients included in this report (Patients 2 and 4) would be expected to improve for reasons unrelated to amantadine administration (recovery from surgery, B12 supplementation). However, spontaneous improvement does not account fully for the observed on-off medication differences. Lastly, the protocol for amantadine administration varied between subjects, which occurs in a clinical setting but may not be appropriate for a prospective study design. The half-life of amantadine (range 10 to 30 hours) limits our ability to state that a therapeutic level was achieved during "on" periods, and that adequate washout occurred when the medication was discontinued for "off" assessments. However, since we observed a significant on-off difference despite this confound, the beneficial effect associated with amantadine administration might be even larger than that we observed.

Amantadine may be particularly feasible for use in rehabilitation, as clinicians are familiar with its use in the setting of brain injury, although for different indications. This medication is widely prescribed for patients with traumatic brain injury, amotivational syndromes, and minimally conscious state, and most rehabilitation professionals are experienced with its use. It is likely that clinicians would be willing to prescribe amantadine for aphasia, were they informed of

possible patient benefit. At present, it is not specifically identified among reviewed agents for treatment of aphasia (e.g. Greener et al., 2001,Klein and Albert, 2004), and it is unlikely that subjects with aphasia or nonfluent speech who have a normal level of consciousness, and who do not have a history of head injury, receive it.

Amantadine's properties are not unequivocably useful to augment rehabilitation, however. It may have anticholinergic or anticholinergic-like effects on attention, thinking and memory (e.g. Postma and Van Tilburg, 1975). We did not note that any subjects in this study experienced impairment of memory or attention while taking amantadine. However, future controlled studies examining for beneficial effects of amantadine in aphasia may want to use verbal memory or working memory assessment as an additional outcome measure, although such instruments are not always sensitive to anticholinergic-induced cognitive changes (Millet et al., 1982).

The results of this preliminary inquiry support the feasibility of wider study of amantadine for treatment nonfluent aphasia symptoms. We propose that investigators plan further studies of this agent. It may be appropriate for future studies to include subjects with nonfluent speech and linguistic, attentional and conative abnormalities, as we did in this study, including sufficient subjects numbers in each category to permit secondary subgroup analysis. We would argue that such a mixed subject group may be appropriate to study, as patients with abnormal speech output may be under-represented in current research focused on measuring language improvement. Linguistic abnormalities associated with motor speech processing, such as syntactic dysfunction, are not quantified on some standard instruments such as the NIH Stroke Scale (Brott et al., 1994. Thus, researchers may systematically under-represent subjects with nonfluent speech in therapeutic studies.

We urge future rehabilitation researchers to work hard to consider all of the cognitive and functional abnormalities associated with nonfluent speech in studies of aphasia therapies. We would advocate including a range of functional outcome measures, systematic impairment assessment (measures expected to improve versus those not expected to improve, measures expected to be sensitive to changes of the magnitude observed), and appropriately blinded assessment. Qualitative observations on and off medication, and family/caregiver assessment, may also be an important part of future research. Traditional impairment measures are more sensitive to changes in performance than currently-used functional outcome measures. Thus, for future studies, functional outcome measures specific to disorders causing nonfluent speech may need to be developed.

Acknowledgements

Study supported by the National Institutes of Health (NINDS, K08 NS 002085 and K02 NS 47099, Barrett; EB00454, Eslinger), and the Henry H. Kessler Foundation (Barrett). We thank the participants in the study, and clinicians who assisted with patient assessments (Kevin Hargrave, MD, B.Lee Peterlin, DO, Claire Flaherty-Craig, PhD, Kari Parkinson, BA, and Aubrey Wright, MD). Christopher Spofford assisted with preparing a preliminary presentation of this data at the 9th Annual Meeting of the American Society of Neurorehabilitation, published in abstract form in Neurorehabilitation and Neural Repair 2002; 16(4): 370–371. Meghan Barnes assisted with preparing the references.

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Table 1

Demographic and performance data for subjects in the current study.

Subject	Sex, Age (yrs) Educ. (yrs) No. of "off" /"on" assessments	Diagnosis	Neuropsych assessment	Brain imaging, other findings	COWA Off/ On amantadine
1	37 yo woman 12 yrs 3 off/ 3 on	Right ACoA aneurysm complicated by vasospasm, right MCA and right putamenal stroke	Left omissions on cancellation, amnesia with confabulation	CT scan: Subarachnoid hemorrhage, intraventricular blood visible, blood in brain parenchyma near ACoA, right middle cerebral artery infaction, LHP	18.67/25.33 (35.7% imp.) p = 0.017, 2-tailed
2	66 yo man 11 yrs 5 off/ 5 on	Left parietal glioblastoma, status post partial resection	Amnesia, poorly-planned, simplified drawings, pallilalic, perseverative motor behavior and planning/ organizational errors consistent with frontal-subcortical dysfunction.	MRI: Post-surgical defect in left parietal cortex, subcortical white matter, and contiguous corpus callosum. RHP, Right grasp	10.80/14.00 (29.6% imp.) p = 0.325, n.s.
3	43 yo man, 12 yrs 2 off/ 2 on	Right internal carotid artery occlusion. Infarction of entire ACA territory and upper branch MCA	Abnormal emotional expression, leftward line bisection, ("ipsilateral neglect") and left arm motor neglect	MRI: Infarction of complete right anterior and middle cerebral artery territory, including caudate and putamen. Hallucinations, LHP	19.50/28.00 (43.6% imp.) p = 0.248, n.s.
4	62 yo man 8 yrs 4 off/ 4 on	Hypertensive left putamenal hemorrhage	Right neglect dyslexia, perseverative speech	CT: Large left basal ganglia hemorrhage (volume not specified). B12 = 17 after 2 weeks oral supplementation, IM supplemented 1 week before beginning amantadine) RHP (v. mild)	1.5/3.5 (133% imp.) p = 0.201, n.s.

Abbreviations: ACA: anterior cerebral artery, MCA: middle cerebral artery; ACoA: Anterior communicating artery; RHP: right hemiparesis; LHP: left hemiparesis; imp. = improvement; B12: vitamin B12 level; IM = intramuscular

Am J Phys Med Rehabil. Author manuscript; available in PMC 2007 August 6.