Critical Review:
Improving effectiveness of speech-language therapy in post-stroke aphasia recovery: Pharmacological options

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This critical reviews examines the use of Piracetam, Memantine, Levadopa, and Dextroamphetamines alongside speech-language therapy in patients with poststroke aphasia. A literature search using computerized databases was completed resulting in six randomized control trials meeting the inclusion criteria. The articles were evaluated using the PEDro scale to evaluate the level of evidence and validity, with a discussion of clinical utility. Results suggest potential for Memantine and Dextroamphetamine aiding in improving overall language measures, Levadopa aiding in improving repetition measures, and Piracetam aiding in improving written language scores. The research presented good validity but has several limitations in clinical utility.

Introduction

Within the realms of treatment of disorders of the cognitive domains, pharmacotherapy leads in both it's utility and efficacy (Small, 2001). Although small scale studies have shown effectiveness of several drugs in improving aphasia symptoms there are currently no drugs widely approved by major drug administrations for the treatment of post-stroke aphasia (Bakheit, 2004). Aphasia treatments have conventionally relied solely on the use of speech and language therapy approaches. Research has sparsely shown the effectiveness of traditional speech and language therapies in improving measures of overall speech and language (Saikaley et al., 2018). This certainly does not mean that they aren't effective, but it may suggest that we should be exploring options to help improve their utility.

Within studies of stroke rehabilitation pharmacological agents have shown greatest effectiveness when used conjointly with more traditional behavioural therapies (Small, 2001). Thus, this project seeks to evaluate and consolidate the current literature on the use of pharmacological treatments in conjunction with traditional speech language therapy treatment approaches.

Methods

Search Strategy

Computerized databases such as PubMed, PLoS, PsycInfo, and Scopus were utilized to search the literature. Keywords used were as follows: [(aphasia) OR (language impairment) AND (stroke rehabilitation)] AND [(drug therapy) OR (pharmacotherapy)]. Further searches were completed using specific drug keywords: [(amphetamines) OR (memantine) OR (donepezil) OR (acetylcholine agonist) OR (dopamine agonist) OR (levodopa)] AND [(aphasia) OR (language impairment)]. Reference lists of previously searched articles were also drawn from.

Selection Criteria

Studies selected must include subjects with post-stroke aphasia. Subjects in both the experimental and control groups must have concurrently undergone speech-language therapy while receiving either drug or placebo treatment.

Data Collection

Included papers were randomized control trials (RCT), with one cross-over RCT. Six studies were included exploring the use of four different medications.

Results

Piracetam

Piracetam is a nootropic GABA derivative, sometimes used as a memory aid in dementia or other cognitive issues. It is available via prescription in Australia and the UK but is unscheduled in Canada and the US (Wishart et al., 2008).

Huber et al. (1997) completed a randomized double-blinded placebo controlled study. The 50 participants were all right-handed native German speakers suffering from left hemisphere lesions. Participants were in the subacute and chronic phases post-stroke event, ranging from six weeks to 36 months. Only individuals scoring below the 75th percentile on the Aachen Aphasia Test (AAT) were included in this study. Participants were randomly assigned to groups given either 4.8g of piracetam per day or a placebo for six weeks alongside intensive speech language therapy. Therapy consisted of 5 one-hour individual sessions and 5 one-hour group sessions a week. Therapy varied to address symptom specific issues in each subject. Participants were tested at baseline and

post-treatment with the Aachen Aphasia Test. The test includes a token test, a repetition task, a written language section, a naming task, and a comprehension component. The researchers used an analysis of variance (ANOVA) to analyze each of 5 subtest scores. At baseline no significant differences existed between the experimental and control group subtest scores. After the 6 weeks all participants showed improvement from baseline, with the mean scores of each subtest greater in the experimental group. There was a significant difference ($p < 0.5$) observed between the experimental and control groups within the written language subtests. No significant differences were seen between groups for any of the other subtests.

This study featured participants, therapists and assessors that were blindly and randomly allocated to their treatment groups, point and variability measures were completed for each subtest and between group scores were analyzed. The level of evidence offered by this study is compelling, featuring a level 7 PEDro scale rating. Researchers were unable to precisely control for the duration of aphasia before entering the trial, the site and size of the cranial lesions, nor the classification of type of aphasia. These were explained as limitations due to size of the group studied, and impact the clinical utility of the results.

Memantine

Memantine is an NMDA receptor antagonist often used in place of or alongside acetylcholine inhibitors like Donepezil in the treatment of Alzheimer's. Memantine is available via prescription only in Australia, Canada, the UK, and the US (Wishart et al., 2008).

Barbancho et al. (2015) completed a randomized double-blinded placebo controlled study. 28 Spanish-speaking participants were all suffered from left hemisphere ischemic or hemorrhagic strokes greater than one year prior to the commencement of the study. For inclusion individuals must have had a diagnosis of aphasia based on scores of <93.8 on the Western Aphasia Battery-Aphasia Quotient (WAB-AQ). The WAB-AQ consists of subtests of spontaneous speech, auditory comprehension, repetition and naming to create a general aphasia severity score. Subjects were randomly assigned to groups to receive memantine or a placebo. Participants initially underwent a three-week titration period before receiving 10 mg of Memantine or placebo twice daily for the following 17 weeks. At weeks 16-18 drug treatment was combined with three hours daily of Constraint Induced Aphasia Therapy (CIAT). Subjects were placed in groups of 2-3 participants according to similarities in symptoms and aphasia severity in order to complete CIAT. Therapy consisted of picture description guessing games between subjects with therapist guidance and reinforcement. Patients were evaluated using the WAB-AQ at baseline, 16, 18, and 20 weeks. ANOVA comparisons and T-tests were completed to evaluate between and within-group variance. At week 16 a significant ($p < 0.5$) increase was seen in WAB-AQ scores for the treatment group but not for control group. The improvement in scores for the drug group at 16 weeks represents the effect of the memantine alone. At week 18 both groups showed significant improvement ($p < 0.5$) in scores, with a significantly ($p < 0.0001$) greater gain for those in the drug group. At 20 weeks scores for both groups remained stable.

This study featured participants, therapists and assessors that were blindly and randomly allocated to their treatment groups, point and variability measures were completed for each subtest and between group scores were analyzed. Adequate follow-up was also completed. The level of evidence offered by this study is highly suggestive, featuring a level 8 PEDro scale rating.

Berthier et al. (2009) conducted a double-blind randomized placebo controlled trial on 28 chronic post-stroke aphasic patients. This study was a precursor to the Barabancho et al. study that followed much of the same procedure. Participants had unilateral ischemic or hemorrhagic strokes and an aphasia diagnosis on the Western Aphasia Battery. Subjects were randomly assigned to groups to receive memantine or a placebo. Participants initially underwent a three-week titration period before receiving 10 mg of Memantine or placebo twice daily for the following 17 weeks. At weeks 16-18 drug treatment was combined with three hours daily of Constraint Induced Aphasia Therapy (CIAT). Subjects were placed in groups of 2-3 participants according to similarities in symptoms and aphasia severity in order to complete CIAT. Therapy consisted of picture description guessing games between subjects with therapist guidance and reinforcement. Following the 20 weeks of drug or placebo treatment participants underwent a four week washout period before undergoing reevaluation. Patients were evaluated using the WAB at weeks 16, 18, 20, and 24. Between-groups comparisons were made with absolute values at baseline and means from baseline at the other times of evaluation. For significant results, Cohen's d was used to determine effect size. Significant improvements were made on the WAB-AQ in the drug over placebo group at weeks 16, 18, 20, and 24. Strong effect sizes were seen at weeks 16, 18, and 20, and a medium effect

size at week 24. When the WAB subtests were analyzed individually the spontaneous speech, auditory comprehension and naming sections showed improvement but no improvement was observed in the repetition subtest.

This study featured participants, therapists and assessors that were blindly and randomly allocated to their treatment groups, point and variability measures were completed for each subtest and between group scores were analyzed. Adequate follow-up was also completed. It should be noted that participants in the placebo group tended to be at a longer time post stroke at baseline. The level of evidence offered by this study is compelling, featuring a level 8 PEDro scale rating.

Levadopa

Levadopa is a dopamine prodrug used in the treatment of Parkinson's disease. It is available via prescription only in Australia, Canada, the UK, and the US (Wishart et al., 2008).

Seniów et al. (2009) completed a randomized double-blind placebo control trial on 39 aphasia patients. Participants were all right-handed Polish speakers who had stroke between two and eight weeks prior to study commencement. Subjects were randomly assigned to groups receiving either 100mg of levodopa or placebo before each therapy session for a total of 15 days over a period of three weeks. Pre and post therapy subjects completed the Boston Diagnostic Aphasia Assessment (BDAE). The BDAE subtests focusing on verbal fluency, naming, repetition, and comprehension were used for the purpose of this study. Therapy sessions were tailored to each participant based on their apparent deficits and focused verbal expression and comprehension. Pre and post treatment scores were analyzed within groups separately using a Wilcoxon signed rank test, and between groups using the Mann-Whitney U test. Following therapy both the experimental and control groups scored significantly higher on all BDAE subtests than baseline. Scores in the drug group were significantly higher ($p < 0.05$) than the placebo group in subtests measuring naming and repetition (Animal Naming, Repetition of Phrases and Sentences, and Repetition of Words). Differences between groups in the remaining subtests did not reach levels of statistical significance.

This study featured participants, therapists and assessors that were blindly and randomly allocated to their treatment groups, point and variability measures were completed for each subtest, and between group scores were analyzed. The level of evidence offered by this study is highly suggestive, featuring a level 7 PEDro scale rating.

Breitenstein et al. (2015) conducted a prospective randomized double-blind placebo control trial with 10 chronic aphasia patients. Participants were all right-handed German speakers with moderate to severe aphasia as defined by the Aachen Aphasia Test. The study featured a cross-over design with two 10 day therapy phases combined with either daily 100mg levodopa/25mg carbidopa or placebo administrations. Following the completion of each phase participants underwent a four week washout period before undergoing the other condition. Outcomes were measured based on a 50-item word naming task taken from a standardized set by the researchers, and the Amsterdam Nijmegen Everyday Naming Task (ANELT). The ANELT has participants complete theoretical conversational scenarios that are rated on two numerical scales of understandability and intelligibility. Testing was completely after each therapy phase, and again at four weeks post. Analyses were completed in the intention-to-treat population, excluding baseline measures that were a priori defined at zero for both conditions. Following the completion of each phase both conditions made improvements that were maintained at the four week follow-up, but there was no significant difference between-groups. These results held true for both the naming task and the ANELT.

This study featured participants, therapists and assessors that were blindly and randomly allocated to their treatment groups, and point and variability measures were completed for each condition. The crossover repeated-measures design lowers the power the study results. The level of evidence offered by this study is suggestive, featuring a level 5 PEDro scale rating.

Dextroamphetamine

Dextroamphetamine is a central nervous system stimulant commonly used in the treatment of ADHD. Dextroamphetamine is a controlled substance only available via prescription in Australia, Canada, the UK, and the US (Wishart et al., 2008).

Walker-Batson et al. (2003) conducted a randomized double-blind placebo control trial with 21 aphasic patients. Participants were all right-handed English speakers who had nonhemorrhagic strokes less than six months prior to study commencement. Subjects were randomly assigned to groups receiving either 10mg of dextroamphetamine or placebo before each therapy session for a total of 10 sessions. Therapy sessions were each an hour in length and focused on auditory comprehension, speaking, reading, and writing equally. Subjects

completed the Porch Index of Communicative Ability (PICA) pre-intervention and at 7 days post treatment. The PICA contains 18 cross modal subtests yielding an overall percentile score. Significant changes in PICA scores were determined by a 15 percentile point gain at post treatment. Following treatment both groups made significant improvements, with significantly greater gains ($p < 0.01$) in the experimental group.

This study featured participants, therapists and assessors that were blindly and randomly allocated to their treatment groups, point and variability measures were completed for each subtest and between group scores were analyzed. The level of evidence offered by this study is highly suggestive, featuring a level 7 PEDro scale rating.

Discussion

Based on the levels of evidence provided in these studies, as determine by their PEDro scale ratings, the following can be concluded in regards to each drugs effectiveness alongside speech and language therapy:

- Piracetam may improve written language but does not show efficacy in improving overall language measures.
- Both Memantine and Dextromphetamine may aid in improving overall language measures.
- Levadopa may improve repetition but has conflicting results on improvement of naming.

Recommendations

Although the level of evidence provided has considerable strength in its validity and potential efficacy, there are several limitations that affect their clinical utility.

- The studies showed variability in amount of time post-stroke treatments were administered.
- There are individual differences in location of lesion/aphasia types of each participant in the studies.
- Studies did not include in depth explanations of therapy protocol. Therapy sessions can vary greatly based on the clinician administering therapy, length of each session, individual vs group sessions, functional level of participants, etc.
- All of the investigated drugs have counterindications in many conditions comorbid with stroke such as hypertension, high cholesterol, diabetes, and heart disease.

More research should be performed in attempt to mitigate these limitations.

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