***Title*: Use of Amantadine in Treating Cognitive and Motor Impairments in Adolescents and Adults with Cerebral Palsy**

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AAAS1907
NCT04273737
PROTOCOL Version 03/21/2022

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1. INTRODUCTION

Cerebral palsy (CP) is a heterogeneous condition due to injury to the developing brain. It is a condition that is often marked by both cognitive and motor disorders as well as increased prevalence of depression and anxiety. While most studies have focused on improving motor dysfunction, fewer have investigated cognitive impairments associated with CP. Dedicating a study to research the pharmacotherapeutic effect of Amantadine on cognitive function in adolescents and adults with cerebral palsy fills an important gap in development of a potential innovative treatment for cognitive deficits.

This study's approach to treatment is aimed at improvement of cognitive function in primarily the adolescent and adult CP population, something that has not been wholly addressed by the research community to date. In the rehabilitation outpatient setting, we have used Amantadine in children and adults with CP for its dopaminergic properties. Amantadine, initially used as an anti-viral drug, is well supported in the literature for its efficacy in treating acute traumatic brain injury (TBI) to improve alertness, arousal, consciousness, mobility and improve rate of recovery. Based on the success of Amantadine in the TBI population, there are implications for its use in the cerebral palsy population because of the similar etiology of brain injury, but in the developing brain. The aim of this study is to determine the effects of Amantadine in primarily adolescents and adults with CP and to compare pre- and post-intervention outcomes related to the primary goal of improving cognitive function, focused on processing speed and attention span. We will also evaluate secondary goals of improving gross and fine motor skills as well as change in mood since Amantadine controls rigidity that could help functional mobility

2. DESIGN

This single center, prospective, open label study will enroll adolescents and adults diagnosed with cerebral palsy, aged 13-65 years, and case-by-case assessment for children under the age of 13 years old, with a target sample size of 10 participants. A baseline assessment of the following domains will be conducted: cognitive function, gross motor & fine motor function, and mood/psycho-social function. Participants will start a daily regimen of Amantadine: dosing 2-5 mg/kg divided by two daily doses (max daily dose of 300 mg). Participants and caregivers will be given a diary to document their perceived effects of Amantadine.

At 3 and 6 weeks, we will repeat the assessments done in the pre-test to evaluate the efficacy of Amantadine. See below for assessment tools, performed as able according to participants' functional status:

1. Cognitive function: NIH Toolbox (Cognitive Battery)
2. Mood: Patient Health Questionnaire-9 (PHQ-9), BRIEF-A
3. Gross motor function: Berg Balance Test, Timed Up and Go, Modified Ashworth Scale, Modified Tradieu Scale, Passive Range of Motion
4. Fine motor function: Box and Blocks
5. Subjective self-assessment: Patient self-assessment of changes in attention, processing and motor skills

2.1 Participants

This single center, prospective, open label study will enroll adults diagnosed with cerebral palsy aged 13 to 65 years, including a case-by-case basis of including those under the age of 13 years old, with a target sample size of 10 participants.

Most subjects will be recruited from Dr. Kim's Physical Medicine & Rehabilitation clinic. Dr. Kim will approach eligible patients in order to explain the study and to determine interest. Other physicians will also approach eligible patients and will explain the study. A brochure/flyer will be presented to each eligible and interested patient, with the study team's contact information on it for their reference. If they are interested and eligible right away, patients will be asked to fill out the consent form and provide us with their contact information so that we can contact them to schedule their initial assessment visit. Other recruitment methods include use of brochures/flyers in other departments in the hospital/CP Center. There will be no screening over the phone or via email.

2.2 Outcome Measures

Primary Question: Does Amantadine have an effect on cognitive function in 10 adolescents and adults diagnosed with cerebral palsy (CP)?
Hypothesis: If 10 adolescents and adults receive Amantadine, then cognitive function will increase/improve.

Secondary Question: Does Amantadine have an effect on fine and gross motor skills, and mood?
Hypothesis: If 10 adolescents and adults receive Amantadine, then there will be increased fine and gross motor skill function and improved rigidity, and mood scores will improve on the PHQ-9.

2.3 Procedures

A baseline assessment of the following domains will be conducted: cognitive function, gross motor and fine motor function, and mood/psycho-social function. Because the PHQ9 assessment asks a question regarding suicide ideality, we will promptly review it each time it is completed, and if suicide ideality is reported, the subject will be provided with appropriate resources. Participants will start a daily regimen of Amantadine: dosing of 2-5 mg/kg divided by two daily doses (max daily dose of 300 mg). Participants and caregivers will be given a diary to document their perceived effects of Amantadine. At 3 and 6 weeks, we will repeat the assessments done in the pre-test to evaluate efficacy of Amantadine.

2.4 Statistical Analysis

No power calculations were made since there is no previous study that used the same population (adolescents and adults), with the same intervention (Amantadine), to find the same outcomes (cognitive and motor function).

The results will be statistically analyzed by using the paired samples t-test on SPSS.

2.5 Potential Risks

Possible adverse reactions to Amantadine: The adverse reactions reported most frequently at the recommended dose of SYMMETREL (5--10%) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1-5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue.

Infrequently (0.1-1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspnea, skin rash, vomiting, weakness, slurred speech, euphoria, thinking abnormality, amnesia, hyperkinesia, hypertension, decreased libido, and visual disturbance, including punctate subepithelial or other corneal opacity, corneal edema, decreased visual acuity, sensitivity to light, and optic nerve palsy. Rare (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eczematoid dermatitis, oculogyric episodes, suicidal attempt, suicide, and suicidal ideation.

Possible risks from assessments: There are minor risks associated with performing the physical assessments listed in this study. During the cognitive and manual assessments, the patient may become fatigued. The study team will advise the test and instruct the patient to rest if signs of fatigue. The patient may rest or terminate the test at any point if they become too fatigued.

2.6 Data Handling and Monitoring

All study data will be collected and stored in a secure and locked filing cabinet that only the research coordinator has the key to, in the locked and secure office of the research coordinator in Harkness Pavilion. The data will also be securely stored on REDCap and CUIMC OneDrive, an encrypted and secure online database that only the Principal Investigator and co-investigators will be given access to.

Patient data and safety will be monitored locally by implementing monthly meetings involving all personnel who are working on the study in order to ensure appropriate data management and patient confidentiality. Data and patient PHI will be stored in a locked cabinet in a locked office only accessible to the study team, and on a secure and encrypted online database that only the study team will have access to.