CRITICALLY APPRAISED TOPIC

Title
“What is the effect of physiotherapy and neurostimulant medication with physiotherapy and placebo on the functional motor recovery of persons who have suffered stroke?”

Reviewer
Theo van Rijn

Search
Resources Selected:
PubMed, OVID, Rehabdata.

Search Strategy:
All English written abstracts or full articles published between 2002 and 2006.

MeSH Terms:
Neurostimulants; stroke rehabilitation; physiotherapy; amphetamines; levodopa.

Date
The searches were conducted between September 20, 2006 and October 30, 2006. This CAT should be reviewed on an annual basis.

Citations:
Approximately 75 citations were found of which 12 were selected and deemed possibly informative. Only one article will be discussed for the purposes of this CAT.

Summary of Study
1. Population:
Patients with an acute unilateral cerebral hemispheric stroke causing a hemiparesis or hemiplegia with a severe or moderate severity (using Fugl Meyer motor scale) were recruited. Patients had to be medically fit to participate in a rehabilitation program, had no significant premorbid disability and could provide informed consent. Exclusion criteria included brain stem/cerebellar stroke; pre-existing deficit that would interfere with assessments; dementia; unstable angina; congestive heart failure; unstable arrhythmia, or uncontrolled hypertension; psychosis; use of an alpha adrenergic antagonist/agonist or monoamine oxidase inhibitors.

2. Interventions:
A total of 10 mg amphetamine sulfate or identical placebo capsules were administered as a single dose followed 90 minutes later followed by a 1 hour physiotherapy session. The first treatment began 5-10 days after the stroke and continued every 3rd or 4th day for a total of 10 drug therapy sessions over the course of
a 5-week period. Drug administration was verified at the time of each scheduled dose and any protocol deviations were documented.

One physiotherapist provided the study treatments for all participants at each of the 5 acute care hospitals or rehabilitation hospitals involved in the study. Treatment was based on neuro-developmental principles of remediation. Assessments were individualized based on a patient’s abilities. Patients were challenged to work at a level just above their ability and assistance with the missing components with normal movement were provided. The amount of physiotherapy provided for standard care was documented for each patient.

3. Outcomes:
The primary measure outcome was the Fugl-Meyer motor scale. All motor assessments were performed by 1 physiotherapist at 13 standardized times: baseline; each of 10 treatment sessions; 3-4 days after the final treatment; at 3 months. All secondary outcomes were measured by 1 physiotherapist and included: FIM; Chedoke-McMaster Disability Inventory (assess mobility); Clinical Outcome Variable Scale to quantify ambulation; Chedoke-McMaster Arm and Hand Activity Inventory to assess upper limb function. A study coordinator monitored the drug using interviews, hospital chart reviews. Any evidence of psychomotor stimulation was recorded. Adverse effects and prescription medications were documented.

4. Results:
Seventy-one stroke patients were recruited and randomly allocated to a treatment group. Thirty-one of the drug treatment recipients completed the study and were followed up at 6 weeks and 36 of the placebo study group were followed up at 6 weeks. By the time of the third month, one person in the treated group had died and 2 had withdrawn due to medical complications. In the placebo group 1 withdrew due to surgical intervention. This left a total of 31 persons in the drug treated group at 3 months. None were lost in follow-up. Thirty-five persons in the placebo group were present at 3 months and 1 subsequently died as a result of stroke.

In general, the two groups were well-balanced with reference to the baseline characteristics and stroke severity. However, in the randomization, the drug treated group in the moderate hemi-paretic portion of the study was significantly imbalanced, based on the Fugl-Meyer scores (the drug treated group were more severely impaired than the placebo treated group).

Repeated analysis of variances over the various time points showed no general difference between the drug treated and placebo group and primary outcome of recovery on the Fugl-Meyer scale for the entire cohort and for the those with severe motor dysfunctions. There was a significant main effect of amphetamine on the upper extremity motor recovery. It was thought that the initial motor score could have favored the drug treated group because of “regression to the mean.” It was pointed out that the natural history of a stroke shows that the recovery rate during the first 6 weeks is often greater for patients with initially more severe hemiparesis.
Because of the ceiling effect of the Fugl-Meyer scale limits, its ability to detect minor changes in milder stroke patients was limited and this may have been the reason why the placebo group didn’t show as good improvement as the stroke group.

**Appraisal**

1. **Validity:**
   This was an interventional study, randomized, double blinded and placebo controlled. I did not undertake any specific statistical intervention. As the results using the specific drug at the dose and timing suggested did not yield any significant difference between the two groups, the NNT cannot be calculated.

2. **Results:**
   The only calculated statistical difference in the various treatment groups involved those whose stroke was classified as ‘moderate’ using FM motor score before and after treatment. There were no other significant differences in any of the various parameters examined. The demographics, stroke lesion characteristics, baseline stroke severity, and outcome follow-up at 6 weeks and 3 months, were not significantly different between groups. The power of the study was not noted; however, the investigators noted the study was the “largest public trial investigating amphetamine-coupled stroke rehabilitation.” The demographics of the entire population, as well as the various sub-populations were outlined in detail. Therapy bias was limited by the fact that only one therapist was responsible for treating each group in each of the various hospitals and rehabilitation centers. Challenges were noted in patient recruitment with about 1 in 40 participation rate due to the various stringent criteria used. The considerable variability in individual recovery following a stroke made the possibility of treatment (however small) difficult to detect above and beyond the natural recovery. Another inherent difficulty was extrapolating animal studies (upon which the current study model was designed) in designing human trials. The dose response curve for amphetamine and its frequency of administration in this situation has never been determined. The type of physiotherapy undertaken may have also been a factor in the lack of response.

3. **Applicability:**
   The prospects of enhancing neuro-recovery with neuro-stimulation drugs have been noted based on animal studies. However, until dose response curves are delineated for drug use, as well as the timing of the drug and frequency of distribution, it would be incorrect to state that the study ruled out a treatment effect under different circumstances. Given the animal models used, further studies should focus on upper or lower limb specific functioning using physiotherapy techniques that were effective, reproducible and could be standardized. This study suggested that in previous studies (involving the same dose and patient populations) ‘positive’ results more likely were based on statistical differences rather than actual treatment effect.
Conclusions
Recovery following stroke is not affected when dextroamphetamine is used in conjunction with physiotherapy, at a specific dosage and timing before treatment. Until proper dose response curves and frequency and timing of neurostimulants are better understood, the use of such drugs in stroke rehabilitation still remains largely empirical.