

Official Title: Effect of tetrabenazine on Stroop interference in Huntington disease

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**Effect of tetrabenazine on Stroop interference in
Huntington disease**

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Protocol, Statistical Analysis Plan, and Results

Specific Aim

Tetrabenazine has been shown to improve gating of abnormal visual stimuli and improve postural stability in Huntington disease (HD) patients as measured by computerized dynamic posturography testing [1]. This study aims to elucidate whether partial dopaminergic depletion via low dose tetrabenazine has a similar effect on masking out of abnormal visual stimuli on the Stroop interference test.

Background

The effect of tetrabenazine on chorea has been well established [2], Additional effects which may not necessarily involve chorea and may involve improvement in information processing of divergent stimuli have only recently been elucidated [1].

This study investigates whether partial dopaminergic depletion via brief administration of low dose tetrabenazine has a beneficial effect on Stroop scores in Huntington disease patients. Showing an improvement in processing of visual stimuli at a lower dose chorea would be an intriguing possibility, further supporting a separate, chorea-independent mechanism for some of tetrabenazine's beneficial effects. Most likely, this is a dopamine related effect involving information processing in the frontal lobe [1]. Dopaminergic blockade in healthy volunteers with haloperidol has been shown to reduce Stroop interference [3]. Dietary dopaminergic depletion in healthy volunteers also reduced Stroop interference [4].

The study is aimed as a pilot study. If results are promising, a larger trial with longer-term administration of tetrabenazine and more frequent, blinded measurements of Stroop interference during the titration period may be considered.

Analysis of raw scores from Stroop testing in the Huntington Study Group trial [2] showed a statistically significant decline in the raw word reading score, but no significant changes in the raw color reading or raw interference scores. Calculated Stroop scores using either the Golden or Chafetz formulae [5] were not reported for this trial. It may be possible that the Chafetz score would properly account for slower word reading in tetrabenazine treated Huntington disease patients and show reduction in interference even if the raw interference score remains unchanged. For this reason, raw as well as calculated interference scores via both formulae will be reported in this trial. A three day withdrawal of steady state high tetrabenazine by Fekete et al. showed a significant effect on the calculated Stroop test [5].

Methods:

Study design:

Ten subjects who are residents of Terence Cardinal Cooke (TCC) nursing home and have an established diagnosis of Huntington disease will be recruited by the principal investigator for participation in this study. Anticipated breakdown subject numbers by sex or ethnic categories is not known.

Key inclusion criteria for the study will be:

1. Established diagnosis of Huntington disease by movement disorders expert
2. Patients not currently taking tetrabenazine as well as those off tetrabenazine for at least three days will be enrolled
3. Patients should not have taken dopamine receptor blocking medication for at least three days (as this has been shown to affect the Stroop score in normals [3]).

The data collection instrument is the standard Stroop color naming, word reading, and interference test.

Stroop test will be administered to patients in the morning to patients who are OFF tetrabenazine (de novo or three day withdrawal). 12.5 mg of TBZ will be administered just after the first Stroop test and also 3 hours later. ON Stroop test will be administered 6 hours after the OFF Stroop test.

The raw word reading, color reading, and interference scores will be recorded and used for further analysis.

Resources:

The study will be conducted at Terence Cardinal Cooke (TCC) nursing home, which has a dedicated wing exclusively for HD patients. The staff members in the HD unit have years of experience in dealing with the challenges of HD care. In addition, they have years of experience of treating HD with tetrabenazine.

Evaluation:

Statistical analysis:

The three raw Stroop scores will be compared between ON and OFF groups. In addition, both Golden and Chafetz interference scores will be calculated, with customary age correction according to established convention. The ON and OFF scores may be compared using paired Student's t-test in the cases of raw scores and Golden calculated scores. Chafetz scores will be compared via Wilcoxon signed rank test.

Power analysis

Given that a study examining effect on Stroop scores in the setting of low dose tetrabenazine administration has not been previously performed, the size of the potential effect is not known and hence direct power analysis is not possible.

The closest study from which to obtain effect size on Stroop test for power analysis is a three day withdrawal of steady state tetrabenazine [6]. Using Glass's d formula:

$$d = \frac{|\text{average}_a - \text{average}_b|}{\text{stdev}_{\text{control}}} = \frac{|14.3 - 7.72|}{7.5} = 0.8773$$

alpha=0.05 for single tailed t test power=1-beta error=0.95 with sample size of 8

as calculated by G Power software

Safety monitoring:

The principal investigator will always be reachable in case of side effects. If an untoward side effect such as worsening of depression does occur after the first dose, the patient will be withdrawn from the study. It is expected that frequency and severity side effects will be low given the low dose and brief period of administration of the study drug. It is important to note that the side effects listed in the prescribing information for tetrabenazine were noted during dose escalation towards higher target doses and are aggregates of side effects during multi-week studies.

References

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Results

Only two patients were enrolled in the study. Their results are not amenable to statistical analysis given low enrollment.