Reviewer's report

Title: Clinical Treatment Reverses Attentional Deficits in Congestive Heart Failure

Authors:

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Version: 2 Date: 24 Aug 2001

Reviewer: Dr Katrina Rayls

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until I see revised version

1.) This is an interesting study as intuitively, one would hypothesize (and probably have anecdotal information) that many patients with a chronic cardiac disease process could improve cognitively as a result of treatment for the disorder. In addition, methodologically sound studies which demonstrate these effects are few. The idea of reversible cognitive effects of medical illness has been well demonstrated in other disorders (e.g. hepatic encephalopathy, systemic lupus erythmatosus).

2.) The authors do not provide a description of the definition of "clinical treatment." I see this as a major problem as the changes in cognitive function are attributed to the "clinical treatment" and there are a number of regularly employed treatments for congestive heart failure. I assume this means that the treatment provided to patients varies according to their specific clinical features. However, it is imperative that the reader has some information about this both for replication of results as well as understanding the potential mechanism by which improvement occurs.

3.) I would like the authors to provide information regarding the tools/procedure used to rule out depression in subjects. They cite ICD-10, however, it would be informative to know whether a structured interview or questionnaires were used. Depression or depressive symptomology is commonly seen in the geriatric population and would easily account for cognitive deficits seen.

4.) It sounds as though in the CHF group, an exclusion criterion was that they not have had a stroke in the past six months, but in the control group subjects were excluded if they had any history of stroke. Given the variability and possible severity of stroke, as well as it's potential impact on cognition, the authors should consider providing some objective information regarding any CHF subjects included with a history of stroke (e.g. localization, severity, chronic deficits). These factors may not only impact treatment response, but also cognitive function (attention/concentration and psychomotor speed) and emotional status.

5.) I have some serious concerns regarding the description of objective measures provided by the authors. Some of these test descriptions fail to provide adequate information regarding the specific tests used making it difficult to interpret the raw data presented. In addition, this lack of clarification makes it
impossible to replicate the study in the future. For example:

a. The description of the Digit Span subtest from the WAIS-R sounds as though the authors are administering only the digits forward component of that test. If this is the case then it needs to be specified so that raw scores are meaningful to any reader familiar with the test.

b. The appropriate name for the "Digit Symbol Substitution" test is the Digit Symbol test. By the description it is fairly apparent (by it's inclusion in the WAIS-R) what test is being described, however, to avoid confusion (like my own in first reading this - I am very familiar with these tests and had to look in Lezak, reference 18, to determine if there was a test called "Digit Symbol Substitution" of which I was unaware) the term Digit Symbol Test should be utilized.

c. The specific Letter Cancellation test utilized is not identified.

d. While the authors state the use of a "simplified version" of the Trail Making Tests, the term simplified is not defined. The definition of the test described in the text sound like the regular versions of the Trail Making Tests. Again, it is difficult to ascribe any meaning to the raw scores when the specific test and/or procedures used are unclear.

6.) Another concern with regard to measures utilized has to do with consistently reporting what the tests purport to assess. For example, it appears as though the most improvement was demonstrated on Digit Symbol and Letter Cancellation tests. It should be consistently noted in the text that these tests assess performance with regard to attention as well as psychomotor speed. As the paper proceeds, the attentional domain receives the most attribution of deficit/improvement. The authors should be careful to include psychomotor speed. In fact, all measures of attention were not significantly improved (Trails A, Digit Span) and the repeated reference to improvement of attentional abilities may be misleading.

7.) It would be helpful if the authors would provide the rationale for the six subjects chosen to receive SPECT studies. One assumes it is based on clinical indication; however, some other set of criteria may have been used. Is this a random subset or has any selection bias been introduced? Without the inclusion criteria the readers are unaware.

8.) Although this is not fixable, the authors on future studies may consider adding some measure of general cognitive function to the post treatment battery such as the MMSE. Attention and psychomotor speed are highly variable and one wonders if there has been any change in cognitive function over time. The MMSE takes only 10-15 minutes and would provide good information. The strongest methodology is probably not to re-administer only tests that tap into domains in which you expect a change in performance, but rather a broader range of cognitive domains.

9.) The authors cite in their discussion as a design flaw the failure to re-assess control subjects following the treatment period. I think this is a tremendous flaw. Both practice effects and fluctuations over time occur in the cognitive measures chosen. Furthermore, control subjects should, as a general rule, engage in the exact same procedures as treatment subjects to ensure comparisons are of value because we cannot assume that what we believe accounts for the changes actually accounts for the changes. It is, therefore, best to eliminate any extraneous concerns that we are able. For example, we cannot say with certainty that an improvement in the weather over the intervening six weeks of treatment does not account for cognitive improvements seen and that had control subjects been retested they would also have shown marked improvements.

10.) The remarkable age difference of subjects concerns me. Although the authors have statistically adjusted for age to compare, I am still concerned, particularly given the magnitude of difference and interpretive significance. For example, the fact that the CHF group (mean age=67.3) fails to demonstrate a significant difference in performance as compared to the control group (mean age 76.7)
is not very impressive. In this age group, over 60, age is the most highly negatively correlated factor with cognitive performance. It would seem, therefore, that an age-matched group would be appropriate here even if it decreased sample sizes.

11.) The authors should be utilizing the exact same groups both pre- and post- treatment. Therefore, those subjects that dropped out/died during the course of the study should not be utilized in the pre-assessment analyses. I believe this is a major flaw in this study. As the authors have written it, they compare:

a. Pre-assessment; 50 CHF baseline vs. 30 controls
b. Post-assessment; 31 CHF baseline vs. 31 CHF after treatment
c. Post-assessment; 31 CHF after treatment vs. 30 controls

Conclusions are unclear as the authors report initial cognitive impairments as compared to controls, which "improve" as a result of treatment as differences abate. This is an unsupported conclusion as the groups pre- and post- are different. The same 31 subjects should be used in the comparison between CHF baseline and controls. This is especially important as the authors found that subjects who dropped out had lower scores on the Digit Symbol test and the Letter Cancellation test - the two tests where significant differences are found between pre and post assessment. Based on estimation in looking at the numbers, the results would unlikely change, but without making the comparison, it is impossible to know.

12.) On page seven in the post-treatment assessment section, the authors state, "...cognitive scores improved for all tasks." While raw scores improve, not all of these differences are statistically significant and, therefore, cannot be stated as improvement.

13.) In Table 1 the authors should specify which statistical test was run (separate columns would be one way of doing this). They should also specify whether the t-value represented is for the homoscedasticity or heteroscedasticity t-test. I assume here that the authors tested whether variances were significantly different and then chose the appropriate t-test. Also, since they conducted some ANCOVA’s, shouldn’t some of the statistics presented be F-values? For the nonparametric ANOVA’s, the test used should be identified on the table per the previous comments.

14.) Ditto for Table 2, where it is stated, "All statistical analyses, but MMSE and CAMCOG, used the Mann-Whitney test." Apparently, ANCOVA was used for the latter two tables.

15.) The authors do not provide adjustments of p-values for the Bonferroni inequality. I suspect this is justified since the outcome variables are likely to be significantly correlated and, therefore, not independent. Spearman correlation analysis was done for EF vs. CAMCOG scores and this association was significant. However, it would be interesting to know whether correlations were significant for other pairs of outcome variables. This might also provide clinical information of interest.

16.) In the first paragraph of the Discussion section the authors should add the word "approximately" to the sentence which states, "In fact, half of the patients had CAMCOG and MMSE." I believe one of the percentages was 44.9.

17.) In the second paragraph of the Discussion section, the authors may wish to cite other factors which have been shown to contribute to reduced cognitive performance such as depression, anxiety, stress, certain medications (cognitive impairments have been shown as a result of digoxin treatment), concomitant medical problems (e.g. Cheyne-Stokes respiration) and others as appropriate.
18.) In the third paragraph of the Discussion section, the authors may want to qualify the following statement, "It seems, therefore, that patients with marked attentional deficits at the time of admission to hospital are at increased risk of death..." This is a very strong statement based on limited data. Instead they may state something suggesting that attentional or cognitive deficit on initial evaluation may provide additional diagnostic information pertaining to severity of congestive heart failure disease stage.

19.) In the fourth paragraph of the Discussion section, the authors report that, "...all attentional scores of patients after treatment of CHF were similar to those of elderly controls." Again, I raise the concern that the elderly controls referred to are significantly older than treatment patients. This might best be stated as cognitive status in some domains (e.g. attention/psychomotor speed) may be remarkably improved as a result of treatment.

20.) The fifth paragraph of the Discussion section addresses potential mechanisms of cognitive disruption in CHF patients. It would, again, be helpful here to discuss the treatment employed, as it would add to this knowledge.

21.) Finally, while this paper is interesting, the data are limited. I have some concerns regarding the strength of some of the statements. For example, the paper is entitled, "Clinical Treatment Reverses Attentional Deficits in Congestive Heart Failure." This is probably a bit strong and should be tempered.

**Competing interests:**

None declared.