Author's response to reviews

Title: Clinical symptoms and performance on the continuous performance test in children with attention deficit hyperactivity disorder between subtypes: a natural follow-up study for 6 months

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Version: 2 Date: 8 February 2011

Author's response to reviews: see over
08 FEB, 2010

Melissa Norton, MD
Editor-in-chief
BMC Psychiatry

Re: Wang et al: Clinical Symptoms and Performance on the Continuous Performance Test in Children with Attention Deficit Hyperactivity Disorder between Subtypes: a Natural Follow-up Study for 6 Months

Dear Dr. Norton,

We greatly appreciate these valuable comments from three reviewers’ on our previous manuscript “Clinical Symptoms and Performance on the Continuous Performance Test in Children with Attention Deficit Hyperactivity Disorder between Subtypes: a Natural Follow-up Study for 6 Months” (MS: 1814985388418219). We have revised the manuscript substantially, and would like to re-submit it for your consideration for publication in the BMC Psychiatry.

Attached are our responses to the issues raised by two reviewers, along with the revised manuscript. We look forward to hearing from you soon.

Best regards,

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Responses to comments from Reviewer #1

Thank you for your comments.

Specific comments:

i. According to both the literature and the data of the current study, aggression and hyperactivity correlate. For example, the factor analysis conducted in this study revealed that opposition and hyperactivity are loaded on the same factor. From a clinical standpoint, despite the overlapping between aggression and hyperactivity, it might be important to know that aggression predicts outcome better than hyperactivity. Nevertheless, from a theoretical standpoint, it is important to control for the overlapping, e.g., by covairating hyperactivity level in the analysis of the effect of aggression.

RE: Thanks for your valuable comments. Barkley et al. (1989) and Matier et al. (1992) investigated methylphenidate (MPH) response in aggressive and non-aggressive ADHD children (Reference 11, 12 in our manuscript). Barkley et al. (1989) divided the study population into aggressive and non-aggressive subgroups by aggressive scale of CBCL (T score > 70). Matier et al. (1992) placed an ADHD child in the aggressive group if at least one of seven items from the DSM-III-R criteria for conduct disorder. These studies analyzed the effects of aggression without using hyperactivity levels as a covariate. To our knowledge, the concerns of these studies were simply to examine the differences for MPH responses between subgroups which were classified by different ways. Similarly, the purpose of our study was to determinate whether there were differences for improvements in ADHD symptoms between classifications by DSM-IV or CBCL aggression scale, rather than a “pure aggressive subtype” without contaminated by hyperactivity level. For these reasons, we did not control other scales possibly correlated to aggression (e.g. hyperactivity, delinquency,…), although aggression and hyperactivity do correlate. Furthermore, we have re-analyzed the data without “oppositional score in the SNAP-IV” from the factor analysis as your recommendations, in the next point. It would diminish the inflation of differences for ADHD symptoms between aggression groups. Thus, we decided to keep the original way of analyses, and hope you can kindly identify our considerations. We added the statements in

Abstract (page 2, line 13-14)

“…, and were additionally categorized into aggressive and non-aggressive subtypes by aggression scale in CBCL for comparisons.”

Discussion (page 12, line 14-15)
“Nevertheless, the interactions of sub-grouping by CBCL aggressive scale with performance in the CPT were significant.”

Limitations (page 15, line 9-10)

“Furthermore, the correlation of aggression and hyperactivity might hinder the distinguishability in predict outcome, so there might be a more valid way to make subgroups.”

Conclusions (page 16, line 4-7)

“The classification of ADHD patients into aggressive and non-aggressive types by aggression scale in CBCL, rather than using the current DSM-IV classification,...”

ii. Surprisingly, baseline differences in clinical hyperactivity between H+/H- is smaller than between A+/A- (see fig. 1B and fig. 2F). I suggest 2 explanations for this: a. Aggression and hyperactivity overlap drastically and in this study aggression provides an extreme operationalization of hyperactivity. Such an explanation hinders the attempt to distinguish between hyperactivity and aggression in prediction MPH outcome. b. The clinical hyperactivity factor includes the opposition subscale of the SNAP-IV. As opposition involves aggression, inclusion of opposition to the factor inflates differences between A+ and A- groups on clinical hyperactivity. Note that clinical hyperactivity was higher across all visits in both H+ compared to H- and A+ compared to A-, but reached statistical significance only in A+ compared to A-. This might be a direct consequence of the inflated differences between aggression groups in clinical hyperactivity. I suggest to repeat the factor analysis without the SNAP-IV opposition.

RE: Thanks for your precious suggestion. We have re-analyzed the data with leaving out “oppositional score in the SNAP-IV” from the principal factor analysis as your recommendations. The weights for the measures of the new four factors are listed in Table 3 (page 29). The statistical results for the new four factors are in the same direction with those in previous analyses. According to the results, we have corrected the statistical values in:

Methods (page 9, line 13-14)

“The ADHD measures, except oppositional scores of SNAP-IV, were reduced by means of a principal components analysis (PCA).”

Results (page 11, line 2-6)

“The resultant factors were labeled on the basis of their clinical meaning: CPT distraction (factor 1), CPT impulsivity (factor 2), clinical hyperactivity (factor 3),
and clinical inattention (factor 4). These 4 factors had eigenvalues of 3.99, 2.21, 1.44, and 1.16, respectively, and accounted for 79.93% of the total matrix variance.”

**Results (page 11, line 7-10)**

“During the 6-month treatment, there were significant improvements in CPT impulsivity (F = 17.22, p < 0.001), clinical hyperactivity (F = 19.85, p < 0.001), and clinical inattention (F = 26.06, p < 0.001). However, CPT distraction was not improved (F = 0.80, p = 0.497), and there were no significant differences between any paired visits.”

**Figure 1, Figure 2 and their legends (page 23 & 24)**

iii. Most importantly, the conclusion regarding the superiority of aggression over hyperactivity is based on the finding that no differences between H+ and H- in clinical and cognitive factor were found, whereas clinical hyperactivity and CPT factors were higher in A+ compared to A-. Along the methods and results sections, the authors report interactions between factors and subtypes. Probably, what they actually mean are interactions between visits and subtypes. Note that on the clinical hyperactivity factor, a main effect of aggression, but no interaction between visits and aggression, was found. Presumably, MPH diminished clinical hyperactivity in both groups in a similar rate, resulting in preservation of baseline differences between aggression groups in hyperactivity level. Therefore, the conclusion of differential effect of MPH on A+ and A- groups is not supported and should be eliminated from the abstract and the discussion.

**RE:** Thank you for this comment. According to the statistical results for new four factors, scores of clinical hyperactivity (factor 3) in both groups do diminish in a similar rate. There were only interactions between visits and subtypes in CPT performance (factor 1 and factor 2). Thus, we have rephrased some part of the **Conclusions (page 16, line 4-7)** and **Abstract (page 1, line 25 to page 2, line 2)** to avoid unsubstantiated speculation.

“The classification of ADHD patients into aggressive and non-aggressive types by aggression scale in CBCL, rather than using the current DSM-IV classification, might be valid for predicting improvements in neurocognitive performance, but not in behavioral symptoms.”

2. Despite the importance of aggression to the clinical picture of ADHD and the
emphasis that was put on this variable as a potential predictor of outcome, the authors did not provide an outcome measure of aggression. This might be overcome by analysis of the opposition measure of the SNAP-IV as an outcome measure.

**RE:** Thanks for your precious suggestion. Since we leave out “oppositional score of the SNAP-IV” from the factor analysis, we use the oppositional score outcome measure of aggression. We have added the information into

**Methods (page 9, line 16-17)**

“The composite score for each factor and oppositional scores of SNAP-IV were applied to the analysis for repeated-measure analysis of variance (ANOVA),....”

**Results (page 11, line 13-15)**

“The oppositional scores of SNAP-IV significantly changed over 6 months (F = 22.74, p < 0.001), and there were significant differences from V1 to V2, and V3 to V4.”

**Discussion (page 14, line 16-17)**

“The hyperactive-impulsive, inattentive and oppositional ADHD clinical symptoms were significantly improved during 6 months.”

3. Minor revisions:

i. The authors may want to provide the number of the H+A+, H+A-, H-A+ and H-A- groups, separately.

**RE:** Thanks you. According to the suggestion of reviewer 2, we split the Combined group and Hyperactivity/Impulsivity groups of ADHD patients. Thus, the distribution of A+, A-, and DSM-IV subtypes showed as following, and we have added these numbers into **Table 2 (page 27)**

<table>
<thead>
<tr>
<th></th>
<th>Aggressive (A+)</th>
<th>Non-aggressive (A-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattentive type</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Hyperactive-impulsive type</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Combined type</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

ii. A power analysis justifying the expected effect sizes and the size of N is advisable.

**RE:** Sample size calculations were based on the setting as the lower limit of clinical significance an effect size of 0.4 (small to moderate), and on the requirement of 80% power and p = 0.05. According to the analyses by software package
GPowr 3.1, the case number should be larger than 41. Thus, we set 50 ADHD patients recruited in our study protocol. However, the dropout rate may have reduced the statistical power. We have added this point to Discussion (page 15, line 13-17)

“Finally, the sample size of our study was not sufficiently large, so the study might not have adequate statistical power to detect possible differences in ADHD symptoms and CPT performance between ADHD subtypes. Meanwhile, the dropout rate may have reduced the statistical power and influenced the results. Caution should be taken in applying the results to clinical practice.”

iii. The CPT first factor is sometimes called "CPT inattention" and sometimes "CPT distraction". Uniformity may make the reading easier.

RE: Thanks for your kindly suggestion. We have unified the name of this factor as “CPT distraction” in the manuscript, in Results (page 11-12), Discussion (page 12), Table (page 29), Figure 1 and Figure 2.

Responses to comments from Reviewer #2

Thank you for your comments.

Specific comments:

1. A major concern is with respect to what is being concluded in this study. The improvement reported in the children with ADHD seems to be attributed to time on medication, as opposed to just medication. Time and medication are conflated in the analyses. Time 1 (baseline) has no medication, whereas the subsequent times have medication. Are the significant effects only from Time 1 to Time 2, or from Times 2, 3, and 4? This is currently unclear in the analyses. Are the effects attributable to time or medication?

RE: Thanks for your precious comments. To make it clear, we stressed the trends of changes for ADHD symptoms over time, and rephrased some sentences in Results (page 11, line 9-13).

“Howeover, CPT distraction was not improved (F = 0.80, p = 0.497), and there
were no significant differences between any paired visits. For the rest three factors aforementioned, the trends of changes were the same during 6 months. There were significant improvements from V1 to V2, and V2 to V3, but no significant differences from V3 to V4."

Indeed, it is difficult to distinguish these improvements attributable to time or medication, because of the limitation of study design. We could only conclude that ADHD patients had symptoms improvements in realistic clinical settings. We have stressed these issues in:

**Limitations (page 14, line 23-25)**

“*In addition, there was no data of ADHD patients on placebo or non-medicated for comparison; hence, we could not certainly justify these results derived from effects of MPH or time.*”

**Conclusions (page 16, line 2-4)**

“We suggest ADHD symptoms, which include impulsivity performance in the CPT and clinical inattention and hyperactivity dimensions, were significantly improved during 6 months in realistic clinical settings.”

2. The fact that NOT a double-blind methodology was used brings into question the meaning of the parent report measures. There was also significant attrition across timepoints. These are major limitations of this study. This may not be revisable, but are noted here.

**RE:** Thanks for this comment. It is certainly the major limitation of this study. Nevertheless, CPT is considered to have advantages over other ADHD evaluation tools by eliminating rater bias and being sensitive for detecting inattention. We stressed these issue in:

**Background (page 5, line 14-16)**

“*First, whether there are sustainable improvements in ADHD clinical symptoms and neurocognitive function in realistic clinical settings.*”

**Discussion (page 12, line 21-22)**

“In general, CPT is a relatively objective index which showed less placebo effects and rating bias [39].”

**Limitations (page 14, line 21-25)**

“*First, this was an open labeled, non-randomized study, so the placebo effects, rating bias, and reporting bias could not be ruled out. In addition, there was no data of ADHD patients on placebo or non-medicated for comparison; hence, we*
could not certainly justify these results derived from effects of MPH or time.”

3. Given that medication was the main treatment in this study, more precise and accurate information should be provided regarding the nature of the medication treatment. Did these children use medication all of the time, what was the adherence to the treatment, and what was the average dose/child based on their weight? Also, how much contact did families have with their psychiatrist? Did that influence the analyses?

RE:
(1) For medication, dosing of MPH in this study followed the recommended dose (0.3-1.0 mg/kg) in the textbook (Kaplan and Sadock’s synopsis of psychiatry; 9th ed. Baltimore: Williams & Wilkins Co., 2003: page 1227). Patients were advised to take MPH at least on weekday; however, drug holiday was permitted. All patients were drug free at V1, and patients were administered MPH at approximately 1 to 2 hours before the CPT were performed at V2, V3 and V4. We emphasized the importance of drug compliance to the patients and their parents, and confirmed the drug compliance at each visit according to the reports of patients’ parents and the remnant drug. There were four patients did not take MPH. We coded average daily doses of MPH at each visit, and we further use the average doses/body weight during 6-month as a covariate in the statistical analyses. We elucidated these issues to:

Methods (page 8, line 17-20)
“Patients were advised to take MPH at least on weekday, but drug holiday was permitted. We confirmed the drug compliance at each visit according to the reports of patients’ parents and the remnant drug.”

Statistical Analyses (page 9, line 20-21)
“We investigated the extent of the differences in changes of these composite ADHD scores for each factor between ADHD subtypes, also by repeated-measure analysis of variance (ANOVA), using average MPH dosage/body weight during 6 month as a covariate.”

Results (page 10, line 16-18)
“The reasons for premature discontinuation were adverse events (N = 3), non-compliance (N = 4), withdrawal of consent (N = 2), and lost to follow-up (N = 11).”

Discussion (page 15, line 11-13)
“Third, the treatment procedure was not standardized, so there was a possible
confounding effect from the MPH dosage, although MPH doses/body weight was used as a covariate in the analyses.”

(2) Contact with families: In general, patients’ families only contacted with their psychiatrist while the patients visited the outpatient department. However, there were no treatment instructions given other than that the psychiatrist should manage the subjects per their usual practice. The frequency of follow-up of these patients was variable, and it might lead to possible reporting bias. We add the statement in Discussion (page 14, line 21-22)

“First, this was an open labeled, non-randomized study, so the placebo effects, rating bias, and reporting bias could not be ruled out.”

4. As inattention is a part of the Combined subtype, it would be useful to split the Combined group and Hyperactivity/Impulsivity groups. There were 11 children who met criteria for the Hyperactivity/Impulsivity group.

RE: Thanks for your valuable suggestion. We have split the ADHD patients into Inattentive, Hyperactive/Impulsive, and Combined group according to the DSM-IV subtype. We re-analyzed the data by this classification. Most of the statistical results for the new classification are in the same direction with those in previous analyses. However, the “clinical hyperactivity (factor 3)” revealed a significant difference between subtypes during 6 months. According to the results, we have re-drawn Figure 1 and corrected the information in:

Abstract (page 2, line 11-12 & line 20-21)

“The ADHD patients were divided into DSM-IV subtypes (Inattentive, Hyperactive-impulsive and Combined type),…”

“The clinical hyperactive symptoms were significantly different between ADHD patients sub-grouping both by DSM-IV and aggression.”

Methods (page 9, line 4-5, line 8)

“The ADHD patients were divided into DSM-IV subtypes (Inattentive, Hyperactive-impulsive type, and Combined type)…."

"The Student’s t-test or One-way analysis of variance (ANOVA) was used to…."

Results (page 10, line 5-7)

“Table 1 presents and compares the demographic data and ADHD symptom measurements of the CBCL, SNAP-IV, ADHD-RS and CPT between DSM-IV subtypes at baseline.”

Results (page 11, line 16-17 & line 20-21)

“In terms of the differences between DSM-IV subtypes, Figure 1 summarizes the
results of changes over time for each of the four dependent factors…..”
“For clinical hyperactivity, there was significant difference (F = 4.11, p = 0.024)
between subtypes, but no significant interactions with DSM-IV subtypes.”

Discussion (page 12, line 10-12)
“There were significant differences in clinical hyperactivity both between ADHD
patients sub-grouping both by DSM-IV subtype….”

Discussion (page 13, line 7-9)
“In our study, there were no interactions of DSM-IV subtypes with these 4
dimensions of clinical symptoms and cognitive performance among ADHD
patients….”

Table 1 (page 25) and Figure 1 legend (page 23).