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Neuropsychological Functioning and OROS® Methylphenidate in an Adult Attention-Deficit/Hyperactivity Disorder (ADHD) Population

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ABSTRACT

Objective: Neuropsychological tests have been used in attention-deficit/hyperactivity disorder (ADHD) to compare ADHD patients with normal subjects, to assess drug–placebo differences in clinical trials and to identify appropriate medication levels via test dose paradigms. While clinical studies have generally been positive[1] with moderate effect sizes, outcomes have been inconsistent, particularly in adults. This analysis examined a neurocognitive battery in a sample of adult ADHD subjects during a clinical trial of OROS® methylphenidate (OROS MPH; Concerta®).[2]

Methods: This 8-week crossover study utilized OROS MPH in 41 subjects who met *DSM-IV* criteria and the Utah Criteria for ADHD. ADHD symptoms were assessed using the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)[3] and the ADHD–Rating Scale (ADHD-RS). (The primary efficacy and safety results were previously reported.[2]) The CNS Vital Signs (CNSVS) is a computer-based neurocognitive battery with tests of Verbal and Visual Memory, Finger Tapping, Symbol Digit Coding (SDC), the Stroop Test, the Shifting Attention Test (SAT), and the Continuous Performance Test (CPT). The developer has reported average scores for both normal and ADHD subjects on these tests.[4] Baseline scores on this population were compared with the normative data. The impact of treatment (OROS MPH vs placebo) on test scores was assessed via paired *t*-tests.

Results: OROS MPH was superior to placebo for all clinical ADHD measures, including total WRAADDS (44% vs 13% improvement; P=0.001), plus the subscales addressing inattention, hyperactivity/impulsivity, and emotional dysregulation. At baseline, our ADHD patients had CNSVS scores midway between the developer's ADHD and normal samples. However, on errors in the Stroop and CTP commission errors, the ADHD patients scored worse than either comparison group. Although OROS MPH was usually associated with better scores than placebo, this difference only achieved significance for 4 of the tests: SDC number correct (P=0.041), Stroop complex reaction time (P=0.009), SAT number correct (P=0.018), and CPT reaction time (P=0.034).

Conclusions: Baseline scores were consistently worse than the test developer's normative data, and endpoint scores on OROS MPH were consistently better than placebo. The tests that reached or approached significance were all test scores that had previously reached significance in test dose paradigms. The longer period between testing in this clinical trial (4 weeks) compared with a test dose paradigm (1 hour) may contribute to the weaker relationship. Conversely, actual clinical trials in adults with ADHD have frequently failed to find drug–placebo differences on cognitive testing.

INTRODUCTION

- Neurocognitive explanations of attention-deficit/hyperactivity disorder (ADHD) often focus on impairment of attention and executive functioning.
- Neuropsychological testing in clinical trials has emphasized
  - Studies comparing ADHD subjects with normal subjects at baseline to identify which measures are most closely related to the illness
  - Clinical trials comparing patients on placebo vs active medication to establish treatment-related improvement or impairment.
- Although studies often report positive findings[1] with moderate effect sizes, outcomes have been inconsistent across studies.
  - There seems to be limited consensus on which neuropsychological tests provide the most useful data.
  - Actual clinical trials have not produced results as strong as in laboratory settings.
- CNS Vital Signs (CNSVS) is a computer-administered neurocognitive screening battery that comprises the following familiar tests: Verbal and Visual Memory, Finger Tapping, Symbol Digit Coding (SDC), the Stroop Test, the Shifting Attention Test (SAT), and the Continuous Performance Test (CPT).[4]
  - Several of these tests have been used in ADHD research.
  - The developers report that this battery yields good reliability and validity.
  - These attributes plus the consistency of computerized administration make it attractive for both clinical and research applications.
- This analysis, from an 8-week, double-blind, placebo-controlled, crossover clinical study of OROS® methylphenidate (OROS MPH; Concerta®),[2] examined the CNSVS neurocognitive battery in a sample of adult ADHD subjects during a clinical trial of OROS MPH.
- The primary efficacy results from the study (Wender-Reimherr Adult Attention Deficit Disorder Scale [WRAADDS], the Adult ADHD–Rating Scale [ADHD-RS], and the Clinical Global Impressions–Improvement [CGI-I] Scale) demonstrated that OROS MPH was effective in the treatment of ADHD symptoms in adults.[2]

OBJECTIVE

- To evaluate the CNSVS in assessing neuropsychological functioning in adult ADHD by
  - Comparing baseline scores in the OROS MPH study population with normative data reported by the test's developer[4]
  - Assessing change in neuropsychological functioning during OROS MPH treatment in adults with ADHD using the CNSVS.

METHODS

Study Design

- This placebo-controlled, double-blind, crossover study of OROS MPH in adult ADHD included 41 subjects.[2]
- There were two 4-week, double-blind periods.
- Subjects met *DSM-IV* Criteria and the Utah Criteria for adult ADHD.
- Following baseline evaluation, patients were randomized to OROS MPH or placebo.
- Medication dose was increased every 2 to 3 days to a maximum dose of 90 mg based on side effects and efficacy in an effort to achieve a maximum tolerated dose by the end of 2 weeks. The individualized maximum tolerated dose was then held constant for 2 weeks.
- Subject samples were assessed for ADHD symptom outcomes measures, CNSVS normative data at baseline, and CNSVS double-blind analyses.

Outcome Measures

- WRAADDS, ADHD-RS, and the CGI-I Scale were used to assess ADHD symptoms in the primary efficacy and safety study.[2]
  - Treatment response was defined as either a score of ≤2 on the CGI-I or improvement of ≥50 on the WRAADDS.
- Four tests from the CNSVS neurocognitive screening battery were used to assess neuropsychological functioning:
  - Symbol Digit Coding (SDC)
  - Stroop Test
  - Shifting Attention Test (SAT)
  - Continuous Performance Test (CPT)

Normative Data

- The developer has reported average scores for both normal and ADHD subjects on the CNSVS tests.[4]
- For this study, some of the CNSVS normative data[4] were revised following personal communications with the developers.

Analysis

- Baseline CNSVS scores in the study population were compared with the normative data.
- Efficacy of OROS MPH on ADHD symptoms was assessed using a mixed models design.
- The impact of treatment (OROS MPH vs placebo) on CNSVS scores was assessed via paired *t*-tests.
  - *t*-Tests were one tailed and significance was P=0.05.

RESULTS

- Of the 41 subjects, 26 were assessed using the CNSVS at baseline, whereas 29 subjects were assessed at the end of both treatment arms.
- Mean age was 28.2 ± 8.9 years.
- 69% of subjects were male.

ADHD Symptoms

- Subjects improved more in the OROS MPH group than the placebo arm using either the WRAADDS (effect size = 0.83; P=0.001) or the ADHD-RS (effect size = 0.63; P=0.003) (**Figure 1**).

Baseline CNSVS scores

- **Table 1** compares the OROS MPH study sample with the developer's normative sample and the developer's ADHD sample in the 4 tests relevant to ADHD.
- This sample resembled the developer's ADHD group more than their normative group.

Figure 1. *Response of ADHD symptoms to treatment.*

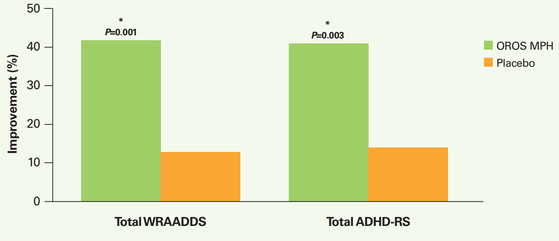

Table 1. *Comparing the Developer's Normal and ADHD Samples with Our Patients at Baseline*

	Developer's Normals[4] (Mean ± SD)	Developer's ADHD Patients[4] (Mean ± SD)	OROS MPH Study Patients (Mean ± SD)	Patients With 1 SD Worse Than Normal (%)
Symbol Digit Coding				
Number correct*	58.8 ± 14.0	54.2 ± 13.5	55.4 ± 12.1	28
Errors†	1.8 ± 3.2	6.6 ± 31.7	1.6 ± 2.1	8
Stroop Test				
Simple RT*†	265.1 ± 62.1	314.4 ± 119.8	308.2 ± 131.8	12
Complex RT*†	586.6 ± 104.5	646.7 ± 124.3	579.0 ± 103.1	22
Reaction time†	691.1 ± 127.3	755.4 ± 153.2	718.1± 106.4	21
Errors†	2.4 ± 2.1	3.4 ± 4.3	4.0 ± 4.7	24
Shifting Attention Test				
Number correct*	50.7 ± 8.8	46.2 ± 10.2	47.9 ± 8.0	20
Errors†	8.9 ± 7.3	12.4 ± 11.4	12.0 ± 11.4	23
Reaction time†	992.9 ± 165.0	1040.2 ± 215.1	1014.3 ± 181.7	9
Continuous Performance Test				
Number correct*	39.7 ± 0.8	38.9 ± 2.2	39.1 ± 2.9	3
Omission errors†	1.48 ± 1.7	3.0 ± 7.5	0.9 ± 2.9	3
Commission errors	0.3 ± 0.6	2.5 ± 5.5	5.5 ± 22.4	9
Reaction time*†	409.9 ± 51.7	460.5 ± 74.5	436 ± 65.6	8

*Items that achieved significance in a test dose paradigm.
†Lower score = greater improvement, less impairment.

- In all but 5 specific test scores, these subjects had average scores worse than the developer's normal group but not as bad as the developer's ADHD group.
- Our sample had more Stroop errors and CTP commission errors than either of the developer's groups.
- At baseline, 72% of subjects had CNSVS scores that were more than 1 SD worse than normal in at least one domain; there were 10 (38%) subjects who had 3 or more CNSVS scores that were 1 SD worse than normal.

CNSVS and Treatment

- Of the 13 specific test scores, 4 demonstrated a positive treatment effect (**Table 2**).
- All 4 (SDC number correct, Stroop complex reaction time, SAT number correct, and CPT reaction time) had achieved significance in a previous test dose paradigm conducted by the test's developers.[4]

Table 2. *Specific Test Scores for CNSVS Tests Related to ADHD*

	Placebo (Mean ± SD)	OROS MPH (Mean ± SD)	*P* Value	Correlations‡
Symbol Digit Coding				
Number correct*	57.4 ± 17.8	60.6 ± 16.7	0.041	0.839
Error†	1.8 ± 2.3	1.2 ± 1.4	0.243	0.154
Stroop Test				
Simple RT†	306.4 ± 90.3	309.2 ± 96.9	0.468	0.219
Complex RT*†	612.0 ± 79.0	580.3 ± 64.1	0.009	0.453
Reaction time*†	708.3 ± 113.2	686.8 ± 99.6	0.148	0.506
Errors†	3.7 ± 4.7	2.8 ± 3.0	0.130	0.425
Shifting Attention Test				
Number correct*	51.3 ± 8.6	54.9 ± 9.6	0.018	0.629
Errors†	9.7 ± 9.0	7.8 ± 10.8	0.085	0.809
Reaction time†	993.1 ± 162.4	968.6 ± 192.0	0.138	0.761
Continuous Performance Test				
Number correct*	37.8 ± 6.4	38.1 ± 6.6	0.400	-0.087
Omission errors*†	2.2 ± 6.4	1.9 ± 6.6	0.400	-0.087
Commission errors†	8.3 ± 28.6	3.7 ± 10.5	0.217	-0.092
Reaction time*†	450.6 ± 93.8	413.5 ± 43.7	0.034	0.118

*Items that achieved significance in a test dose paradigm.
†Lower score = greater improvement, less impairment.
‡Correlations between the placebo and OROS MPH arms.

- Although some specific test scores (SDC number correct, SAT number correct, and SAT errors) showed great consistency between the 2 treatment arms, other specific test scores (SDC errors, CTP number correct, CTP omission errors, CTP commission errors, and CTP reaction time) had very low correlations. These low correlations differ substantially from reported test–retest reliability.

CONCLUSIONS

- Although 72% of the subjects demonstrated impairment in some area, this impairment was not focused on any specific test or domain. Thirty-eight percent of subjects had 3 or more CNSVS scores that were 1 SD worse than normal.
- Treatment-affected CNSVS scores improved in the expected direction with scores in the OROS MPH arm consistently better than placebo; however, most differences did not achieve significance.
- The specific test scores that reached significance (SDC number correct, Stroop complex reaction time, SAT number correct, and CPT reaction time) had previously reached significance in a test dose paradigm.
- In several key measures (the domains of Attention and Cognitive Flexibility plus the CPT test), there were very small correlations between the 2 treatment arms. Although this may be due to treatment, it may be that these measures are simply more unstable for ADHD patients as a group.
- The CNSVS shows promise in assessing neuropsychological functioning in adult ADHD.

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