# A novel methodology for monitoring pharmacological-treatment effects for adolescents and adults with attention-deficit disorder with hyperactivity in general practice

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Abstract
A Quick Test of Cognitive Speed (AQT) provides a novel method for monitoring dose-effects and establishing dose-optimization for adolescents and adults with ADHD, treated in general practice. The AQT processing speed measures, recorded as total naming time (s), probe reactive and active attention and cognitive overhead. Multicenter studies validated that these measures can differentiate the effects of incremental methylphenidate doses, establish a point of reference for dose optimization, and identify non-responders to medication. Here we report the updated results from controlled dose-monitoring of 70 previously medicated adults with ADHD to illustrate the methodology. Sixty-three patients responded to treatment with methylphenidate based on reductions in naming times. Single-dimension color and form naming, with 40 randomized visual stimuli each, indicated minimal changes in reactive attention with incremental methylphenidate doses. Color-form and shift cost measures, probing active attention, indicated significant improvements first with low-dose and then with high-dose methylphenidate. For close to 50% of the responders, measures of active attention (color-form) and cognitive overhead (shift cost), calculated as [Color-Form s – (Color s + Form s)] were optimized and within the average-normal range after low-dose methylphenidate. Increasing methylphenidate doses beyond the point of dose optimization did not result in further improvements of measures of reactive or active attention or cognitive overhead. With high-dose methylphenidate, the active attention and overhead measures were reduced to within the average-normal range for all but two patients. Treatment effects were compared with methylphenidate and atomoxetine for a small sample and indicated no statistical differences. The results suggest that in general or psychiatric practice color-form combination naming times and shift costs can provide proxy measures for active attention during treatment with methylphenidate or atomoxetine.


 

Background and aim

In general practice, it can be difficult to monitor the effects of pharmacological treatment for adolescents and adults with attention-deficit disorder with hyperactivity (ADHD) quantitatively, as many neuro-psychological assessments are time consuming or require the involvement of highly trained professionals for administration or interpretation. Whereas qualitative measures and interviews provide insights into a patient's personal experiences with a specific medication and dose amount, it can be difficult and time consuming to determine if or when an optimal dose has been reached for a given patient. Similarly, it can be difficult to assess whether changes in the timing of the ingestion of medication or of dose amount might result in improved active attention and more efficient over-all functioning during the day or evening hours.

Processing-speed deficits are a part of the ADHD symptomatology that may persist from childhood through adulthood and are known to respond to methylphenidate or atomoxetine [1, 2, 3, 4]. Recent research supports that ADHD can and does emerge during adolescence or adulthood in from 1-10% of diagnosed patients [5]. Currently used, quantitative processing-speed tests for screening and monitoring ADHD vary in design and applicability to general practice. Some processing-speed tests require administration and interpretation by neuropsychologists [6], personnel not generally available in general practice. Others, such as the iconic Stroop Color-Word Test [7], require some level of literacy and these skills are influenced by culture and education, and in some societies by gender. The processing-speed measures in A Quick Test of Cognitive Speed (AQT) [8, 9], the focus of this report, require no reading skills and feature a limited naming vocabulary, which extends the applicability across medical settings. AQT can be administered in standard printed form or by using a new digital version that presents the stimuli, records naming times, calculates standard and T-scores, interprets results, and provides a permanent record [10, 11]. The design uses visual stimuli with four basic colors (*black, blue, red, yellow*) and common geometric forms (*circle, line, square, triangle*). These are presented in randomized order with 40 stimuli on each of three test plates, either as colors, forms, or color-form combinations. The color and form tests probe reactive attention and reflect reaction, retrieval and response time. Color-form combinations probe active attention, a central executive function [12], with added cognitive demands on attention, working memory and set-shifting (cognitive control). Research, including neuroimaging, of healthy adults and elderly adults with dementia of the Alzheimer's and Lewy Body types, indicate that the AQT color-form naming times may be considered proxies for underlying neurological functions associated with bilateral, posterior temporal-parietal and subcortical activation [10, 11, 13, 14, 15]. Normative data for healthy speakers of English, Danish, and Swedish, ages 15-95 years, suggest that naming times do not differ for speakers of these Germanic languages [8, 9]. In comparison, normative data for Italian and Spanish speakers indicate slightly longer naming times that


 

reflect differences in syllable length [16, 17]. With these features, the AQT tests can complement qualitative assessments that are commonly used in general practice and can provide an alternative for baseline screening and monitoring dose-effects during the pharmacological treatment of, among others, English and Spanish speakers with ADHD. Because treatment effects are evaluated against baseline measures, the test can also be used for speakers of other languages such as Arabic or Japanese.

The use of AQT in general practice receives support from reported statistical characteristics of the test. Thus, between ages 17 to 60 years of age color-form naming times increase minimally at a rate of + 1s per decade and after age 60 years by +1 s per seven years for healthy adults [18, 19]. These findings agree with other evidence that the greatest decline in processing speed in typical aging occurs around the age of 60 years [20]. For healthy adolescents and adults, test-retest reliability coefficients (Pearson r) range from .91 to .95 for color-form naming and support a high degree of stability across assessments [8, 9]. For adults with ADHD, the test-retest reliability coefficient (r) for the active attention measure (color-form naming) improves significantly from .89 at baseline without medication to .94 with optimum methylphenidate [21]. Other data indicate no gender bias for healthy American or Scandinavian adults and that naming times are not subject to learning effects with repeated trials [8, 9, 18]. For adults with ADHD, a recent evaluation of gender bias indicated statistical differences without medication and males used longer times than females [21]. However, at endpoint with high-dose medication there was no statistical gender difference in naming times for adults with ADHD. Independent studies have also established significant concurrent validity between the active attention measure (color-form) and commonly used cognitive and neuropsychological tests [22, 23].

The AQT processing-speed tests have been used in multi-center studies with a variety of clinical groups with ADHD [24, 25, 26, 27, 28]. These studies indicate that the naming time measures can monitor and differentiate dose effects during pharmacological treatment of ADHD and identify non-responders to medication. Furthermore, the dual-dimension measure of active attention (color-form) and the derived measure of cognitive overhead (shift cost), dependent on administering the color, form and color-form tests concurrently, can establish a reference point for dose optimization and for determining potential changes in dose amount or timing [27, 28, 29].

The objective of this review is to present an updated record of findings obtained from continuing studies of monitoring methylphenidate or atomoxetine dose effects during the treatment of adolescents and adults with ADHD. The research methodology is described with reference to dose-monitoring and dose-optimization studies. The clinical methodology, appropriate for general practice, is described with reference to a comparison of dose-effects of sequential treatment with methylphenidate and atomoxetine.

Monitoring methylphenidate dose effects

*Participants* – Patients included in the updated, controlled dose-monitoring study signed informed consents according to the Declaration of Helsinki and its amendments. The studies were approved by regional authorities in the Kalmar Region of Sweden and followed the EU directives on diagnosis and treatment of adults with ADHD [30]. Prerequisites for inclusion were that patients must have (a) Swedish as primary/native language, (b) a diagnosis of ADHD according to Swedish standards, (c) no substance abuse at the time of study, (d) no evidence of psychosis, (e) no or well-controlled diabetes or thyroid dysfunction, and (f) IQ at 80 or above. ADHD diagnoses were determined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000) and the International Classification of Diseases and Related Health Problems (ICD-10) (World Health Organisation, 2003). Seventy previously medicated adults, between ages 17-54 years and with from 8-17 years of education, met criteria for participation. At intake, ASRS-v.1.1 ranged from 20 - 65 (M = 41.48). Three patients were diagnosed with ADHD attentive type (F90.0C) and 67 with ADHD combined type (F90.0B). Of the latter, about 13% presented with comorbidities primarily in the forms of depression (F32.0, 32.1, 32.9).

*Methods* -- Resident psychiatrists at the regional centers administered the tests individually, during scheduled annual reviews. The tests were administered over a period of three/four days, after two days (weekend) off medication in a three-step monitoring procedure first without medication, then with low-dose and finally with immediate-release (IR), high-dose methylphenidate (Medikinet IR). The research methodology required the AQT color, form and color-form tests to be administered twice in standard sequence to assure familiarity with the task and the second set of measures was used for data analyses. Total naming times (s) provided the bases for evaluating statistical differences in processing-speed and efficiency after the ingestion of each of the two controlled, incremental doses of methylphenidate IR.

The test administration without medication occurred early in the morning, after two days without the prior-prescribed medication, to obtain a reference baseline. For the low- and high-dose treatments, patients ingested two equal doses of immediate-release methylphenidate hydrochloride tablets (Medikinet IR), either 10 or 20 mg, equivalent to 8.65 or 17.30 mg methylphenidate. AQT was administered between 45 and 55 minutes after each ingestion, as Medikinet IR tablets take effect between 30-60 minutes after ingestion and effects persist from one to four hours. Of the 70 patients, 23 % received a maximum dose of 17.30 mg methylphenidate (i.e., 20 mg Medikinet IR) and 77 % a maximum dose of 34.60 mg methylphenidate (i.e., 40 mg Medikinet IR), determined based on prior prescribed dose amounts.

*Data analysis* -- One-way ANOVA with post hoc analysis (Scheffe), using StatPlus:macPro v5.9.92 (Analyst Soft Inc., Walnut, CA), compared naming times across treatments, converted to lognormal


 

(ln) when normality was rejected. Changes in shift-cost values were analyzed with non-parametric statistics (Chi-square). Null hypotheses for main effects were rejected at the $p < 0.01$ level of significance to avoid bias and for the post-hoc statistics (Scheffe) at the $p < 0.05$ level.

*Results* -- Initial case-by-case review of the naming times obtained across treatment conditions indicated that 10% obtained repeated naming times within +/- 3 s for color and form and within +/- 5 s for color-form combinations or equal to +/- 1 SD, as compared to healthy adults ages 15-54 years. These patients were considered to be non-responders to medication. The individual means for the non-responders at baseline without medication and with low- and high-dose methylphenidate were all within the average normal range (i.e., < +1SD) as compared to norms for healthy age peers [9, 10, 11].

Sixty-three participants were judged to be responders to methylphenidate, as they exhibited reductions in color-form naming times and shift costs greater than -1 SD compared to normative data [10, 11, 19]. The descriptive statistics for this group are presented in Table 1 and box plots in Figure 1 illustrate the distributions and changes in color, form and color-form naming across treatments. Without medication (baseline), the means for color, form, and color-form were at the upper limits of the normal range but the standard deviations were larger than average-normal. Compared to norm-referenced scores for healthy adults between ages 34-54 years, the prevailing age range for the sample of responders, the mean SS for color-form naming at baseline was 76 and the T-score 33. After high-dose methylphenidate the mean standard score was 104 and the T-score 53, indicating an increase of more than +1SD for both (i.e., 15 and 10 points, respectively)[10,11].

**Table 1.** Means and standard deviations for color, form and color-form naming times and cognitive overhead (shift cost) (s) by treatment condition for 63 responders to immediate-release methylphenidate.

| | *Color* | | *Form* | | *C-F* | | *Overhead* | |
|---|---|---|---|---|---|---|---|---|
| *Medication* | *Mean* | *(SD)* | *Mean* | *(SD)* | *Mean* | *(SD)* | *Mean* | *(SD)* |
| *None (baseline)* | 25.08 | 6.50 | 29.31 | 7.55 | 58.29 | 12.50 | 3.87 | +/-8.38 |
| *Low dose* | 22.29 | 5.30 | 24.99 | 6.11 | 50.63 | 11.54 | 3.32 | +/-8.22 |
| *High dose* | 20.71 | 3.59 | 22.54 | 4.19 | 44.86 | 7.45 | 1.60 | +/-5.17 |

*Average-normal ranges for ages 17-54 yrs. (n = 270):* Color < 25 sec; Form < 30 sec; Color-Form < 55 sec; Overhead < +/-5 sec.


 

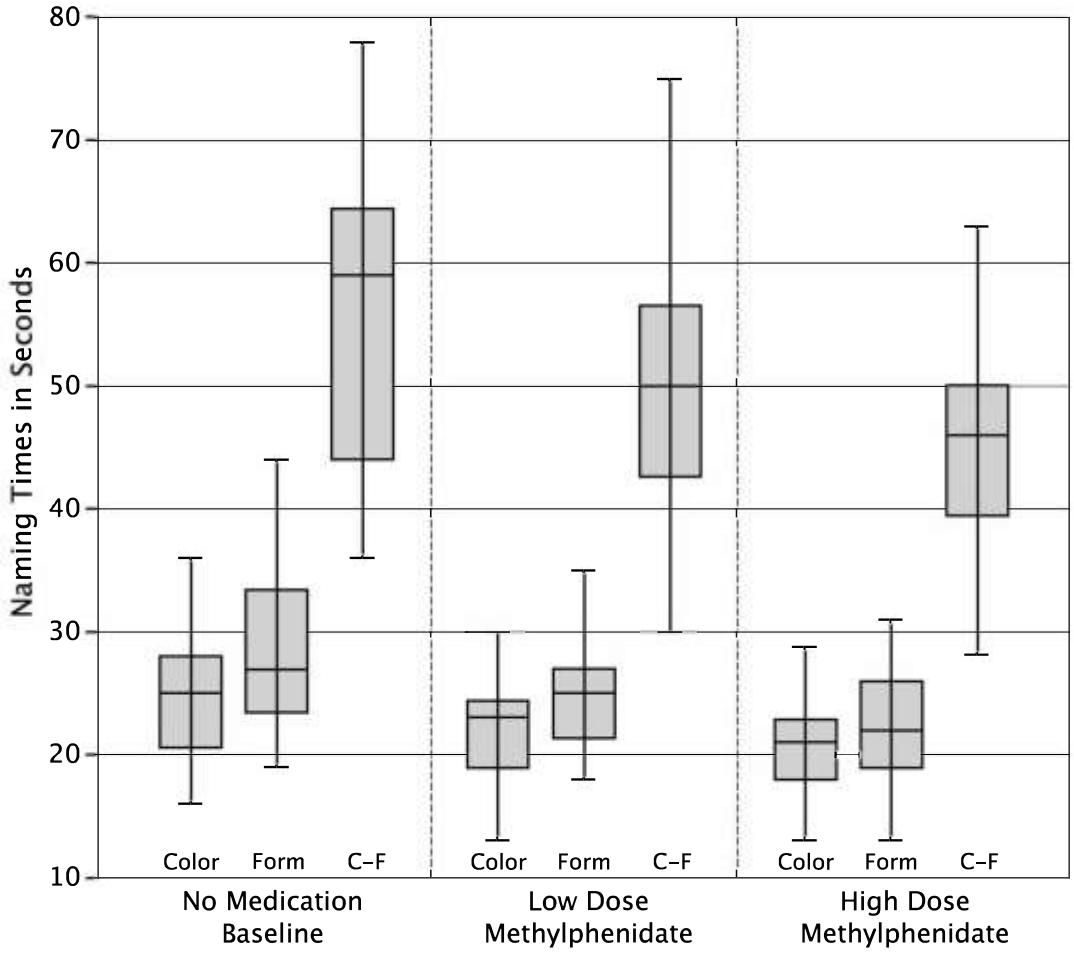


**Figure 1.** Box plots for color, form and color-form naming times for responders to medication at baseline without medication, and with low- and high-dose methylphenidate IR (n = 63).

The mean shift-cost value (overhead) without medication (M = 3,87, SD = +/- 8.38) was in the larger-than-normal range for healthy adults ages 17-54 years (i.e., >+/-4 s) [31]. With low-dose methylphenidate, the color, form and color-form naming-time means were reduced to well within the average-normal range. However, shift costs remained in the larger-than-average range [31]. With high-dose methylphenidate, the means and standard deviations for naming-times and shift-costs were further reduced, but the average shift cost remained slightly larger than the mean for healthy adults ages 17-54 years (i.e., >+/- 4 s) [31].

One-way ANOVA with post hoc analysis (Scheffe), after lognormal (ln) transformation, indicated significant treatment effects for color ($F_{2, 186} = 10.95$; $p < 0.001$; $\eta^2 = 0.10$), form ($F_{2, 186} = 23.19$; $p < 0.001$; $\eta^2 = 0.20$), and color-form naming ($F_{2, 186} = 2\ 5.59$; $p = 0.001$; $\eta^2 = 0.22$), and with medium to large effect sizes for form and color-form naming. Post hoc analysis for color naming indicated longer naming times without medication than with low-


 

dose (Scheffe = 2.95; $p < 0.01$) or high-dose methylphenidate (Scheffe = 4.62, $p < 0.001$). Form naming times were also longer without medication than with low-dose (Scheffe = 4.14; $p < 0.001$) or high-dose methylphenidate (Scheffe = 6.75; $p < 0.001$). For color-form combinations, the naming times again proved longer without medication than with low-dose (Scheffe = 4.02; $p < 0.01$) or high-dose methylphenidate (Scheffe = 7.13: < 0.001). In addition, there was a statistical difference between the low- and high-dose medication conditions (Scheffe = 3.11; $p < 0.01$).

For shift costs (overhead), nonparametric analyses ($\chi^2$ corrected for ties) indicated differences between treatment conditions ($\chi^2$ =7.92; $p = 0.019$) that approached the statistical <0.01 level set a priori. Shift costs were ranked highest without medication, second highest with low- and lowest with high-dose methylphenidate (see Table 1). It should be noted that the average-normal shift cost (s) for healthy adults can range from positive to negative between +/- 4 s. Longer than average negative shift costs can occur if either the color or form times or both are longer-than-normal, as illustrated in the example: color = 32 s, form = 41 s, color + form = 73 s; color-form = 65 s, shift cost = -8 s. In this study larger-than-normal negative shift costs (i.e., >-1SD/-4 sec) were recorded for 16% of participants.

Thirty responders (47.6%) reached normalization and showed maximum treatment effects for color-form naming with low-dose methylphenidate, based on criteria that the low- and high-dose measures differed by +/-3 s or less (i.e., < 1 SEM for healthy adults). For this group, naming times for color-form at baseline, with one exception, were within the average-normal range (M=51.97 s; SD = 8.0 s). For the responders, who needed high-dose methylphenidate for dose optimization, the color-form mean at baseline was in the longer-than-average range (M = 63.33 s; SD =13.42 s). Linear regression plots of the individual color-form naming times (s) for responders (n = 63), with exclusion of one data point for a patient with a baseline color-form measure of 104 sec., are shown without medication, and with low- and high-dose methylphenidate in Figure 2. This allows for comparison of each responder's gains in color-form naming time across treatments.

We considered whether the color-form naming times without medication might predict the amount of gain (s) in color-form naming with high-dose methylphenidate. The average gain for the group (n = 63) was 13.11 s (SD = 7.54) and was larger than -1SD/5 s of the mean reported for healthy adults [19]. Correlation analysis (Pearson r) evaluated associations between baseline naming times and individual gains in color-form naming speed with high-dose methylphenidate. The correlation between baseline color-form naming times and gains in naming speed proved significant ($r = 0.75$; $p = 0.007$) and indicated a large effect size.


 

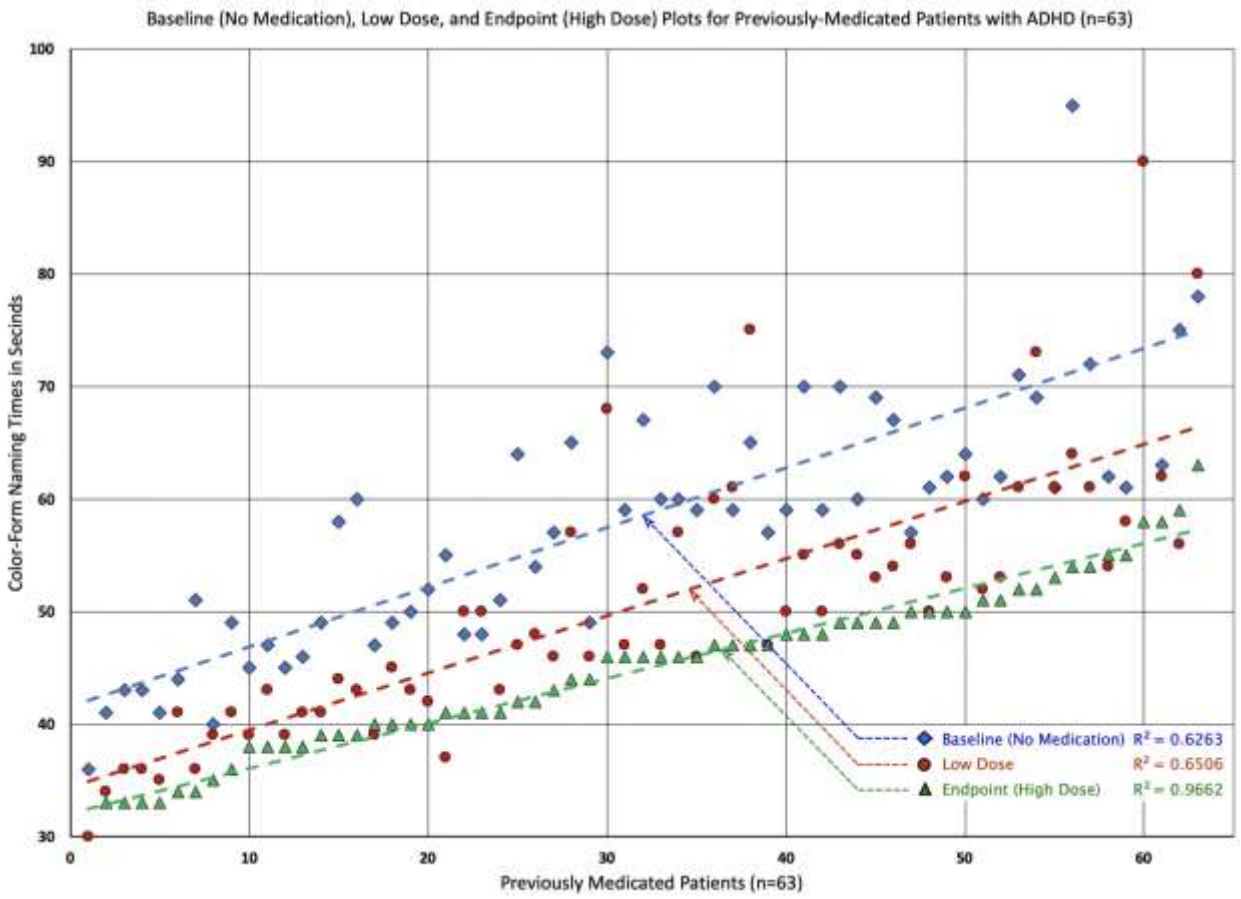


**Figure 2.** Plot of AQT color-form naming times for responders to medication without medication (circles), low-dose (diamonds) and high-dose (squares) methylphenidate IR (n = 63).

Previous studies reported preliminary evidence of the clinical utility of the AQT tests, when used to screen previously medicated adults with ADHD [27, 28]. To evaluate the sensitivity for this group, criterion cut-offs for longer-than-normal naming times for form (i.e., > 30 s) and color-form naming (i.e., > 55 s) and larger-than-normal shift costs (i.e., > 5 sec.) were applied to the baseline measures. The criteria identified 79% of the previously medicated responders in this study as having probably ADHD.

Comparing methylphenidate and atomoxetine

In general-medical or psychiatric practice, pharmacological treatment of ADHD may be prescribed with methylphenidate or atomoxetine. In a follow-up pilot, 13 additional patients received clinical evaluations to compare the ability of the AQT to monitor treatment effects with either medication type. Patients were evaluated with the AQT tests, first after stabilization with methylphenidate, and then after changing to atomoxetine (Strattera). Patients ranged in age from 17 to 41 years and ASRS V1.1 ranged from 22 to 56 (M =


 

39.46) at baseline. Patients in this group experienced impaired academic achievements, difficulties with employment, and exhibited co-morbidities such as mild personality disorders and/or depression. All signed informed consents in accordance with the Declaration of Helsinki and its amendments and the EU directive for Good Clinical Practice was followed.

The clinical protocol for evaluating treatment effects differed slightly from the research protocol in that patients were scheduled for weekly visits. Psychiatric interviews and AQT assessments were administered weekly to monitor the effects of the change in medication type. The AQT tests were administered only once during each visit as patients were already familiar with the procedure. Atomoxetine doses were increased with the patients' acceptance after shared evaluation and discussion by patient and psychiatrist and concurrent monitoring with AQT. Stabilization of the ADHD symptoms with atomoxetine was determined in collaboration, based on evidence of positive effects on behaviors and quality of life. After treatment with atomoxetine, ASRS-V1.1 improved considerably and ranged from 11 to 36 points ($M$ = 22.00). The clinical record of the weekly AQT test results for a representative participant is illustrated in Table 2. The descriptive statistics for the group (n = 13) are provided in Table 3. At baseline, the means for color and form were slightly above the average-normal ranges (i.e., > 25 and > 30 sec., respectively). In contrast, the means for color-form and shift costs (overhead) were in the atypical/pathological range (i.e., > 70 and > 10 sec., respectively) [19, 31]. After the initial treatment with methylphenidate, the means for color, form and color-form were in the average-normal range and the mean shift cost was in the slightly larger-than-normal range (i.e., > 6 sec). After subsequent treatment with atomoxetine, all group means were well within in the average-normal range, based on normative criteria and the comparative outcomes differed by less than 1 SD for each measure (see Table 3).

**Table 2.** Illustrative weekly treatment protocol for a 19-year-old male with ADHD (F90.9).

| *Medication* | *Color* | *Form* | *Color-form* | *Overhead* |
|---|---|---|---|---|
| *None (baseline)* | 29 sec. | 44 sec. | 70sec. | -3sec. |
| *Methylphenidate 30 mg* | 22 sec. | 23 sec. | 55 sec. | 10 sec. |
| *Methylphenidate 50 mg* | 20 sec. | 20 sec. | 48 sec. | 8 sec. |
| *Atomoxetine 50 mg* | 18 sec. | 23 sec. | 44 sec. | 3 sec. |
| *Atomoxetine 60 mg* | 17 sec. | 20 sec. | 43 sec. | 6 sec. |
| *Atomoxetine 60 mg* | 20 sec. | 21 sec. | 41 sec. | 0 sec. |


 

**Table 3.** Means and standard deviations for color, form color-form and cognitive overhead (shift cost) by treatment condition for 13 patients treated first with methylphenidate and then atomoxetine.

| | *Color* | | *Form* | | *C-F* | | *Overhead* | |
|---|---|---|---|---|---|---|---|---|
| *Medication* | *Mean* | *(SD)* | *Mean* | *(SD)* | *Mean* | *(SD)* | *Mean* | *(SD)* |
| *None (baseline)* | 28.85 | 12.79 | 30.85 | 7.30 | 73.69 | 11.26 | 1.00 | +/-3.83 |
| *Methylphenidate* | 22.00 | 3.83 | 25.15 | 3.34 | 53.69 | 8.27 | 5.85 | +/-4.06 |
| *Atomoxetine* | 21.92 | 4.15 | 20.00 | 2.31 | 48.46 | 8.23 | 4.00 | +/-4.16 |

One-way ANOVA, with post hoc analyses (Scheffe), using ln transformed naming times, indicated main effects for color ($F_{2, 36}$ = 4.98; $p$ = 0.0135; $\eta^2$ = 0.22), form ($F_{2, 36}$ = 9.02; $p$ = 0.0007; $\eta^2$ = 0.33), color-form ($F_{2, 36}$ = 24.49; $p$ < 0.0001; $\eta^2$ = 0.58), and overhead (shift cost) ($F_{2, 36}$ = 9.38; $p$ = 0.0001; $\eta^2$ = 0.34) and effect sizes were large. Post-hoc analyses (Scheffe) indicated a statistical difference for color naming between baseline and endpoint of treatment with atomoxetine (Scheffe 2.97; p = 0.02). Form naming showed a statistical difference between baseline and endpoint of treatment with both methylphenidate (Scheffe 2.79; p = 0.03) and atomoxetine (Scheffe 4.17; p = 0.0008). For color-form naming and shift costs (overhead) there were statistical differences between baseline and endpoint after treatment with methylphenidate (Scheffe 5.09; p < 0.0001 and Scheffe 2.84; p = 0.0001, respectively) and with atomoxetine (Scheffe 6.71; p < 0.0001 and Scheffe 4.25; p < 0.0001, respectively). There were no statistical differences between any of the AQT measures after treatment with methylphenidate or atomoxetine. On average, color-form naming speed was shortened by 27% and shift costs (overhead) decreased by 53% after treatment with methylphenidate and by 33% and 71%, respectively, after treatment with atomoxetine.

## Discussion

The findings from this larger dose-monitoring study support earlier reports that the AQT processing-speed time measures for color, form and color-form and the derived shift-costs should prove effective for establishing a reference point for dose-optimization in general practice. In the larger sample of responders to medication, close to one half of patients responded maximally to low-dose methylphenidate and the naming time and shift cost measures were not further reduced with high-dose medication. For the remaining patients, high-dose methylphenidate was needed to optimize and normalize the measures of active attention (color-form) and cognitive overhead (shift costs). In previous dose-monitoring studies with fewer patients (i.e., n = 53 combined), about one third responded maximally with low-dose and two thirds maximally with high-dose methylphenidate [27, 28]. We consider both estimates to be tentative but suggest that monitoring dose effects with AQT may serve to avoid prescribing excessive

medication past the point of dose optimization or normalization.

We did not anticipate any significant treatment effects on the measures of reactive attention with low-dose methylphenidate. Earlier studies indicated that significant improvements of reactive attention (i.e., shorter color or form naming times) occurred only after ingesting high-dose methylphenidate [27, 28]. We anticipated that low-dose methylphenidate would result in improved measures of active attention by showing shorter color-form naming times and smaller shift costs, and that further improvements would occur with high-dose methylphenidate. In this analysis, the significant differences in the active attention measures (color-form and shift costs) between the low- and high-dose treatment conditions were therefore unexpected. Based in the present findings we make no assumptions that the positive effects on the active attention measures might be reflected in every-day behavioral, vocational, or academic improvements, as there were no concurrent or longitudinal evaluations of improved daily-life functions.

With a relatively large sample of adults with ADHD, who responded to medication, we questioned whether color-form naming times without medication might predict the amount of gains (s) in this measure of active attention with high-dose methylphenidate. Subsequent analysis resulted in a correlation coefficient (Pearson r) with a large effect size. The variance estimate indicated that slightly more than half of the gains in active attention could be predicted from the color-form measures at baseline without medication. The predictive ability of using color-form naming times at intake without medication to estimate potential treatment effects on active attention after dose optimization should be explored in further studies.

The sensitivity of using the color-form and shift-cost measures to identify referrals with probable ADHD was also evaluated. Results indicated that 80% of the responders to methylphenidate were identified as having probable-ADHD, based on color-form naming times in the slower-than-normal range and/or derived shift costs in the larger-than-average range, compared to norms for healthy age peers [19, 21]. The level of sensitivity observed in this update compares to earlier findings for previously medicated adults, identified by the screening criteria to have probable ADHD [19, 21]. In comparison, studies of medication-naïve adults resulted in the identification of 90% of patients as having probable ADHD, indicating greater sensitivity for that clinical group [32, 33]. The results support that the AQT color-form naming times and derived shift costs may be used as proxy measures for active attention (i.e., attention, visual working memory, and response shifting) for screening and dose optimization during the treatment of adolescents and adults with ADHD. To respond to current clinical practice, the AQT-assessment protocol would need to be adapted for periodic monitoring of dose effects, either weekly after the onset of pharmacological treatment with either methylphenidate or atomoxetine, or during required annual reviews.

The outcomes of the expanded dose-monitoring study generated a question, considered to be of clinical relevance,

addressed in a follow-up pilot study. It concerned whether the AQT processing-speed and the derived shift-cost measures would result in similar outcomes for a group of patients treated with optimum doses of methylphenidate and subsequently with atomoxetine. In the comparison of the relative effectiveness of using AQT to monitor methylphenidate or atomoxetine dose effects, the assessment protocol corresponded to general practice standards with weekly visits. The purpose was not to compare the relative effectiveness of the two medication types, but to evaluate if AQT would register similar treatment outcomes. The results indicated comparable improvements of reactive attention, assessed by color and form naming, and of active attention, assessed by color-form naming and shift costs. The patients' weekly protocol and the statistical outcomes suggested that the AQT tests may be equally effective in monitoring dose effects during the pharmacological treatment of ADHD with either methylphenidate or atomoxetine.

With the introduction of a novel paradigm for monitoring and optimizing methylphenidate, atomoxetine and other relevant medications for ADHD it seems relevant to question the potential time and cost benefits of adopting the methodology. AQT is fast and easy to administer by using a new web-based version of the test "AQT online" that works on all standard platforms (mac/pc, iPad/tablet) with a screen size above 10 inches. The administration takes about 5 minutes for a typical test session and the tests can be re-administered for monitoring dose effects within hours rather than after days or weeks. The online version presents the stimuli, records naming times, and interprets results, providing a record of the test results in both seconds, standard scores and t-scores for comparison with other psychometric tests, and also stores an audio recording of the test session for documentation. Thus, the test can add objective measurements to the screening and evaluation of ADHD and the regular control of treatment effects. The online version of AQT can be acquired at no initial cost and subsequent payments are based on a pay-per-use concept.

The online version of AQT can be administered in clinical settings, with a health-care professional present, or through remote testing as a self-evaluation in an at-home setting. A staff member, such as a nurse, can be trained to administer AQT online in about one hour and can then develop efficiency in administration in follow-up practice. In everyday practice, however, the primary clinical advantage of using AQT is the ability to make a direct comparison between the baseline time measures without medication and the naming times obtained after medication, and in that way the patient becomes his/her own control. In the pre- and post-medication comparison, changes in color-form combination naming time longer than +/- 6 s and in shift costs (overhead) larger than +/- 4 s are significant, as they represent one standard deviation of the normative mean for healthy adults [19, 21]. By establishing an individual's baseline performance for future comparisons, differences caused by the severity of the problem, the presence of comorbidities, or of unspecified developmental factors or language


 

differences can be minimized. From the patient's and the physician's perspectives, estimating a preliminary methylphenidate or other ADHD relevant medication dose within hours, instead of after days or weeks, is a distinct advantage in that a tentative medication can be prescribed immediately. The effectiveness of the preliminary dose prescribed can then be monitored and adapted in follow-up interviews and assessments after a short period of use. AQT online can also monitor the effectiveness of potential changes in medication type with pharmacological advances or in determining dose timing throughout the day as a means of promoting the patient's functionality during the day and evening hours.

We acknowledge several limitations associated with the study, among them that patients in the updated sample were not followed longitudinally with behavioral ratings or other evaluations of improved functioning in daily life. Secondly, the sample used to compare the effectiveness of the AQT tests for monitoring pharmacological treatment with methylphenidate and atomoxetine was relatively small. Whereas it allowed for statistical analyses, it did not allow for a definitive and unequivocal statement that AQT functions equally well for monitoring methylphenidate or atomoxetine effects. The combined results of the update with a larger patient sample concur with previous observations [27, 28, 29]. They strengthen the conclusion that the cognitive speed (color-form) and cognitive overhead (shift cost) measures may serve as proxies for active attention (i.e., attention, visual working memory, and response shifting) during the pharmacological treatment of adolescents and adults with probable ADHD.

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Conflict of Interest

Authors Niels Peter Nielsen M.D. and Elisabeth H. Wiig Ph.D. co-authored A Quick Test of Cognitive Speed (AQT) in collaboration with Professor Lennart Minthon M.D., Ph.D., University of Lund, Sweden. The copyright is held by AQT Assessment ApS, Copenhagen, Denmark and the co-authors will receive a share of future royalties.

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