Monitoring stimulant-medication effects in adults with attention deficit disorder with hyperactivity with AQT processing speed: A commentary.

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Abstract

This commentary introduces research on monitoring the effects of stimulant medication in 40 adults with ADHD. A Quick Test of Cognitive Speed (AQT) measured the effects of standard low- and high-dose immediate-release methylphenidate within a short time period. Results identified 33 responders and 7 non-responders. For responders, single-dimension (color and form) and dual-dimension (color-form) naming speed increased significantly with high-dose medication and performance profiles were normalized compared to neuro-typical adults. Findings validated prior research and suggested that the procedure and AQT measures might identify the dose point at which normalization occurs after a medication dose has been increased.

Background

In clinical practice, the process of arriving at the optimum dosage of stimulant medication for adolescents and adults with attention deficit disorders with hyperactivity can be time consuming and may require repeated psychiatric consultations. In the article *"Processing speed can monitor stimulant-medication effects in adults with attention deficit disorder with hyperactivity"* [1] we presented a follow-up study that used processing-speed measures [2, 3] to observe the effects of incremental doses of stimulant medication on cognitive speed and set-shift costs, aspects of the symptomatology associated with ADHD.

Previous research with A Quick Test of Cognitive Speed (AQT) [2, 3] indicated that a large majority (i.e., about 90%) of adults with ADHD exhibited significantly slower cognitive speed and larger set-shift costs (overhead) during dual-dimension color-form naming than neuro-typical adults [4-6]. These characteristics also differentiated adult psychiatric referrals with and without ADHD [7]. The findings suggested that a combination of reduced attention, working memory, set-shifting, and cognitive control, reflected in longer color-form naming times and larger shift costs, might characterize adults with ADHD. We then conducted a validation study in which we compared AQT processing speed measures in adults with ADHD without medication and with prescribed stimulant medication (methylphenidate) [8]. The results indicated that cognitive speed was significantly increased and set-shift costs significantly reduced and generally normalized [4, 5], when the same adults received their prescribed doses of stimulant medication (methylphenidate). One of the limitations of the study was, however, that the prescribed variants and doses of the stimulant medication were not controlled. This led to the design of a standard test protocol that introduced incremental doses of immediate-release methylphenidate (Medikinet IR) in association with repeated measures of processing speed within a period of a few hours. We hypothesized that the incremental doses would result in significantly shorter naming times, especially for color-form naming, and that the associated shift costs would decrease significantly; hypotheses that were confirmed.

Methods

For the study we recruited 40 patients, previously diagnosed with ADHD according

to Swedish standards and who had received stimulant medication for a minimum of six months before the study. We developed a standard test protocol that measured processing speed (sec) for AQT color, form and color-form naming at four points over a four day period, each associated with a short psychiatric status interview. Of the tests, each features a plate with 40 visual stimuli consisting of randomly repeated colors (blue, black, red, yellow), forms (circle, line, square, triangle), and combinations of colors and forms (e.g., blue circle) [2, 3]. Set-shift cost, indicating processing efficiency, was calculated using the formula [color-form – (color + form)]. AQT is norm referenced, naming times increase minimally with age (about 1 sec/decade) [4], and there is no evidence of learning or habituation with repetition [2]. The tests were administered (a) with prior prescribed modified-release stimulant medication before the study began, (b) after two days (weekend) without medication, and on the same day (c) with low-dose immediate-release medication within 45-55 min of ingesting 10/20 mg Medikinet IR, and (d) with high-dose medication within 45-55 min of ingesting an additional 10/20 mg Medikinet IR.

Results

Among the patients, there were 33 responders to medication for whom the changes in color-form naming times were larger than one standard deviation (i.e., >6 s) [4] across treatments. One-way ANOVA, using lognormal transformation of naming times, indicated significant treatment effects for all processing-speed measures: Color ($F_{2,96}$ = 5.21; $p > 0.01$; $\eta(2) = 0.10$), form ($F_{2,96}$ = 6.07; $p < 0.01$; $\eta(2) = 0.11$), and color-form ($F_{2,96}$ = 11.18; $p < 0.01$; $\eta(2) = 0.20$). Post hoc analyses (Scheffe) indicated significant increases in processing speed with high-dose medication for color from 24.94 s (SD = 6.53) to 20.45 s (SD = 4.14) (Scheffe = 5.02; $p < 0.01$) and form naming from 28.97 s (SD = 9.96) to 22.39 s (SD = 4.26) (Scheffe = 12.03; $p = 0.01$), compared to the non-medication condition. For color-form naming, measures with increased demands on attention, working memory and cognitive control, processing speed increased significantly, compared to the non-medication condition, from 58.97 s (SD = 15.09) to 51.30 s (SD = 13.27) with low dose (Scheffe = 3.12; $p < 0.05$) and further to 44.06 s (SD = 7.8) with high-dose medication (Scheffe = 11.81; $p < 0.01$). There was no

statistical difference between the low- and high-dose conditions (Scheffe = 1.19; $p > 0.05$). Shift-cost values were reduced from an average of about 8 s to less than 2 s and normalized with high dose medication, compared to norms for neuro-typical adults ages 15-54 [5].

We identified 7 non-responders for whom naming times (sec) for all measures changed minimally (i.e. within +/-3 s) across treatments. Among non-responders, two presented with depressive disorders (F32.9; F41.2), and one each with Asperger's syndrome (F84.5), cluster headache (G44.0), obsessive-compulsive disorder (F42.9) or sleep apnea (G47.30), and one illegally used amphetamine. These comorbidities may have influenced the initial diagnoses or the responsiveness to methylphenidate.

Conclusions

The study validated previous observations of the effects of stimulant medication on cognitive speed (color-form naming) and processing efficiency (shift cost) [8]. In the earlier study with medication-naïve adults with ADHD, we observed that cognitive speed for color-form naming increased and shift costs assumed normal levels for neuro-typical adults [5]. We obtained similar results in this study, but in addition we observed significant increases in perceptual speed (lower color and form naming times) with high-dose medication.

The results we consider of the greatest clinical importance in this controlled study were that the responders' cognitive speed increased incrementally with increased dosage. In the high-dose medication condition, both cognitive speed and shift costs were reduced to normal levels (i.e. <3 s) for every participant [3, 4, 5], suggesting that the dose might have been optimized. It was also notable, that for 8 responders all measures were normalized after ingesting the low dose and that the added dose had insignificant effects (< 3 sec) on cognitive-speed and shift-cost. These observations suggested that the procedure and AQT measures might identify the dose point at which normalization occurs after a medication dose has been increased. From a functional perspective, the cognitive changes observed should result in greater productivity [9] in work and daily-life settings and indirectly in a better quality of life. Whereas the protocol was designed for use with immediate-release stimulant medication, it may be adapted for use with modified-release stimulant medication. We recognize that the test model and associated procedures should

be validated in future research. For future validation research, the senior author has designed a 7-point dose-titration model in which immediate-release methylphenidate is administered with 30 min intervals in incremental doses of 10 mg each, starting with no medication and ending with a total dose of 60 mg. In clinical practice, his protocol has resulted in a performance-curve for color-form naming (sec) in which the points of the greatest cognitive speed and lowest set-shift cost converge to indicate the optimal dose. Additional medication beyond the point of convergence has been observed to result either in no changes or in slower naming times and larger set-shift costs [10].

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