CHAPTER 3

Biomarkers of acute methylphenidate effects in children and adolescents with attention-deficit/ hyperactivity disorder

Submitted

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ABSTRACT

Despite the extensive use of methylphenidate (MPH) and considerable research, suitable validated biomarkers for monitoring the effects of MPH are not currently available. Here, we performed a systematic literature review to identify generally applicable biomarkers for monitoring the effects of immediate-release MPH (MPH-IR) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). We identified 78 randomized placebo-controlled clinical studies that investigated central nervous system effects following a single dose of MPH-IR in pediatric ADHD patients. Neurocognitive clusters and individual tests that were used in five or more studies were evaluated for reporting consistent MPH effects. The following outcomes showed a consistent response to a therapeutic MPH dose across studies based on different cohorts: Continuous Performance Test, Go/no-go Task, Visual Evoked Potentials, and several observation scales (including Following Rules Observations, Oppositional Behavior Observations, On-Task Behavior Observations, and Impulsivity Behavior Observations). A closer inspection of the Visual Evoked Potentials revealed that MPH mediates increases in late potential amplitudes. MPH's effect was best detected in tests and observations regarding motor control, sustained attention, divided attention, and impulsivity (inhibitory control), indicating that MPH has acute effects on all three core symptoms of ADHD among MPH-responsive children with ADHD. These candidate biomarkers should be investigated further in future studies to obtain a more thorough evaluation of dose-response relationships, including their effect size and potential applicability for predicting the response to MPH.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder among children and adolescents. ADHD is characterized by the childhood onset of symptoms that include inattention and impulsivity/hyperactivity[1,2]. The psychostimulant methylphenidate (MPH) is the most commonly prescribed medication for treating the symptoms associated with pediatric ADHD[3,4]. This treatment has been validated by numerous controlled studies that show the efficacy of low-dose oral MPH at reducing the behavioral symptoms associated with the disorder; the effects are usually reported by the child's parents and teachers and include both the cognitive (inattention and impulsivity) and non-cognitive (hyperactivity) domains. In controlled clinical trials, approximately 60-70% of treated children show clinical improvement[5], although the response rate is lower (approximately 50%) and less predictable in clinical practice. The clinical use of MPH is usually based on a trial-and-error approach before optimal therapy is achieved; this approach is often used because MPH's effects vary widely between individuals in terms of clinical response[6] and pharmacokinetics (PK). More than 30% of patients do not respond favorably to MPH at any dose[6] and therefore must switch to an alternative medication after the initial titration phase. As a consequence of this lack of response, a significant percentage of ADHD children either experience a considerable delay in receiving adequate treatment or stop seeking treatment altogether. Therefore, there is a need for a more sensible, personalized therapeutic approach to ADHD.

Despite its long history of use, MPH's precise mechanism of action remains poorly understood, complicating the assessment of treatment efficacy or the timely identification of non-responders. MPH is available in several formulations, with a variety of delivery mechanisms that result in changing PK and effect profiles throughout the day[7]. Immediate-release MPH (MPH-IR) has been on the market for more than 50 years, whereas other formulations have only recently become available. MPH-IR is a short-acting compound, with an onset of action within 30-60 minutes and reaching peak clinical effect 1-2 hours after administration; the effects typically last 2-5 hours. The relationship between MPH's PK and biological effects is complex and not completely understood; however, recent studies suggest that the drug's principal clinical effects closely follow its predicted PK profiles[8,9]. The autonomic, psychomotor, and neurocognitive effects of MPH-IR in pediatric ADHD have been studied extensively. However, previous published studies of the effects of MPH-IR have yielded conflicting results due to several sources of variability, including a lack of standardized biomarkers and effect measures for MPH[10,11]. Despite the widespread use of MPH and extensive research, no validated or generally accepted biomarkers for MPH's effects in children and adolescents with ADHD have been identified. Identifying suitable biomarkers will help researchers develop a more efficacious and specific treatment regimen for children with ADHD; for example, biomarkers could be used for the early identification of responders versus non-responders, to identify patients with an increased risk of developing adverse side effects, and to monitor treatment outcome. Biomarkers could also facilitate future research regarding the core pathology of ADHD, MPH's mechanism of action, and the effects of stimulants in children. The following operational criteria have been used in the search for a suitable biomarker[12–16]: 1: a clear, consistent response across studies using different study cohorts; 2: a clear change in the biomarker in response to a therapeutic dose of MPH; 3: a measurable dose-response and/or concentration-response relationship; and 4) a plausible relationship between the biomarker, the pharmacology of MPH, and the pathogenesis of ADHD.

Here, we performed a systematic review of the literature to investigate generally applicable outcome measures in response to MPH-IR treatment of children and adolescents with ADHD. Our research group and other groups have successfully used this approach in healthy volunteers to identify suitable functional biomarkers for antipsychotic drugs[12], benzodiazepines[13], selective serotonin reuptake inhibitors[14], tetrahydrocannabinol[15], MDMA (i.e., ecstasy)[16], and alcohol[17].

Methods

Search strategy and data collection

To identify studies that investigated the acute effects of MPH in pediatric patients with ADHD, the databases PubMed, EMBASE, and PsycINFO were searched (for the search queries, see Table 1). All returned citations were imported in a Reference Manager database, and duplicate records were removed from this database. Potentially relevant studies were selected by viewing the titles and abstracts. Non-relevant reports were discarded, and the full-length articles of all relevant or potentially relevant reports were obtained. The following inclusion criteria were then applied to this pool of potentially eligible studies: studies that were randomized, double-blind, placebo-controlled clinical trials; studies that compared the effects of an acute dose of MPH-IR versus placebo in previously MPH-treated or MPH-naïve children and/or adolescents with ADHD; studies with a minimum washout period of five half-lives; studies with a minimum cohort size of ten subjects per treatment arm; and studies that were published in English. To minimize population heterogeneity, studies that included subjects with mental retardation (IQ <70) and studies in which ADHD patients were selected for a specific comorbidity were excluded.

Data were extracted from the studies to a pre-established database template (Microsoft Excel). The extracted data included information regarding the study details (e.g., study design, number of subjects, wash-out period), subject characteristics (e.g., gender, age, ADHD type, comorbidity, previous exposure to MPH), medication given (e.g., formulation, dose), and outcome measures (e.g., the type of test, time interval between drug administration and the test, overall effect). Because effect measures and MPH doses varied among the studies, each effect measure at a certain MPH dose was considered an independent effect measure. Thus, the total number of effect measures evaluated was the combined sum of the number of studies, tests, and MPH doses.

Data analysis

Outcome measures were clustered to groups of related tests or test variants (referred to as 'clusters') in order to generate a reasonable degree of standardization across studies and tests. For example, the Arrow/Sound (In) Compatibility Task, Dichotic Listening Task, Divided Attention Task, and Dual Task were clustered under 'Divided Attention', which is part of the functional domain 'Attention'. This approach enabled us to preserve individual study data in the early stages of our analysis, thus enabling us to evaluate individual frequently used tests using uniform outcome measures. We then performed a progressive condensation of the results into logical clusters, thus providing a more general assessment of the drug's effects on groups of comparable tests or functional domains. This approach enabled us to evaluate the practical suitability of using a test as a biomarker in small-to-medium size studies. No effort was made to further quantify the level of statistical significance. Neurocognitive and neurophysiological tasks were categorized into clusters of related tests or test variants[12] using the compendiums of Strauss[18] and Lezak[19].

The clusters were further divided into six domains (referred to as 'domains') in accordance with the Strauss compendium[18], including executive functions, memory, attention, motor function, language, and perception. Physiological measurements (e.g., heart rate, blood pressure, pupil size, and electrodermal activity) were not included in this review. Event-related potentials (ERPs) and neuroendocrine measurements (e.g., cortisol, growth hormone, and prolactin) were also grouped into clusters and domains.

With respect to ERPs, the following clustering method was used. A potential is evoked using a standard visual or auditory stimulus and an infrequent deviant stimulus (the 'target' in the Continuous Performance Task, Go/no-go task, and Oddball task). If the pattern of the potential evoked by the standard stimulus was significantly altered following MPH treatment, the event was classified as a significant effect of MPH on the neurophysiologic parameter (drug condition

x standard stimulus), regardless of the direction of the effect (i.e., a positive or negative wave, increased or decreased amplitude, or a change in time). In addition, if the pattern of the potential evoked by the deviant (or target) stimulus was altered significantly after MPH and compared to the standard stimulus (drug condition x standard stimulus x deviant stimulus), the response was considered to reflect an effect of MPH in the task-related neurocognitive domain (for example, sustained attention in the event of an ERP with the Continuous Performance Task) and was clustered as such in the database.

In several studies, subjective measures and rating scales were used to assess the effect of MPH in children with ADHD. Clustering of these measures was guided by a review of classification methods in published rating scales (the Conners Rating Scale[20] and scales derived therein, and the ADD-H Comprehensive Teacher Rating Scale[21]) and the clusters and domains that are used to classify the neurocognitive tasks[18,19]. This subdivision is described in the Results section.

In our analysis, we assumed that in most cases, no single consistent quantitative outcome parameter could be recorded for an individual test due to the large variation in methods and parameters. Therefore, the ability of a test to reveal a statistically significant difference between placebo and baseline was scored as '+' (an improvement or increase), '=' (no significant effect), or '–' (an impairment or decrease). Different parameters of a single test were grouped if they provided information regarding a common functional cluster. Several tasks yielded different outcome parameters, in some cases showing opposite effects of MPH. If these opposite responses were part of the same neurocognitive cluster, two items were scored for the same test (e.g., one '+' and one '-'). In cases in which one of the improved parameters was part of a different functional cluster than the parameter that did not improve, both items were scored separately (i.e., as belonging to separate clusters). Items that were considered to be secondary test parameters were marked with an asterisk in the database. For example, in the Continuous Performance Task, the level of commission errors (which evaluates impulsivity) is secondary to the level of omission errors (which evaluates sustained attention). These secondary parameters were clustered separately in secondary clusters. However, if a secondary parameter could be categorized in the same functional domain as the primary test parameter, it was not included separately, and only the primary item was added to the database.

For each outcome measure and functional cluster, we calculated the percentage of improved (+) or impaired (-) test outcomes relative to the total number of tests. Secondary outcome measures/clusters and ERP-related clusters were evaluated separately. Consistent MPH-induced improvement in task performance, rating, or observation was defined as an increase in >60% of the tests.

Dose-effect relationships

On average, the clinical dosing range for MPH is linearly correlated with the reduction in ADHD symptoms[22]. The likelihood that a given test will detect a difference in effect between MPH treatment and placebo is expected to increase with increasing dose. Therefore, to investigate MPH's dose-effect relationship, the doses were categorized as 'low', 'medium', or 'high'. The 'low' dose was defined as 0.1-0.25 mg/kg (i.e., the recommended daily therapeutic starting dose), the 'medium' dose was defined as 0.25–0.59 mg/kg, and the 'high' MPH dose was defined as ≥0.6 mg/kg[23]. Dose-effect relationships were measured for clusters and for effect measures that were used in ≥3 studies (per dose category) and/or across ≥15 studies. Dose-related changes in the average percentages of improvement were reported without formal statistical analyses.

Results

Identified studies

The literature search included all scientific articles that were published through December 31, 2009. The search yielded a total of 1,973 hits, from which

78 articles were identified that met the inclusion criteria for this review. Ten of these articles did not explicitly mention DSM or ICD criteria when describing the study population; however, these studies did mention the use of other diagnostic methods (for example, questionnaires, interviews with parents, etc.) to confirm the presence of a hyperactivity disorder. The majority of studies included boys ranging from 5-13 years of age, and the majority of studies investigated a 'medium' dose of MPH (defined as 0.25-0.59 mg/kg; see Methods). The study characteristics are summarized in Table 2.

Clustering of outcome measures

The identified outcome measures – categorized by functional cluster and domain – are summarized in Table 3. Results from domains and clusters that were used only once or twice could not be generalized, and will not be discussed further. In total, 151 separate outcome measures (i.e., tasks and observations) were used to assess the effect of MPH; 104 of these measures were used only once. Only 11 measures were used more than five times, with Visual Evoked Potential and the Go/no-go Task being the most frequently used measures (each was used in ten studies). Progressive condensation of outcome measures resulted in 49 clusters.

Following MPH treatment, task performance and observations generally improved. Only four of the 78 studies reported performance impairment or decreased hormone serum levels following MPH; these four outcomes were the Math Cheating Task[24], the Behavior After Failure Task[25], the Tachistoscopic Task[26], and Prolactin levels[27].

The outcome measures that were used in at least five studies (Table 4) were reasonably consistent (>60%) at detecting MPH's effects across studies (with the exception of the Arithmetic Task and the Reaction Time Task). The tests with the highest consistency were Visual Evoked Potentials and the Continuous Performance Task (with 84.2% and 76.2% consistency, respectively). With respect to the observational outcome measures, the following observation scales had the highest consistency, ranging from 68.4-100%: Following Rules, Oppositional Behavior, On-Task Behavior, and Impulsive Behavior. The only scale that did not improve consistently across the studies was Social Behavior. None of the outcome measures that were used in at least 5 studies showed impairment following MPH treatment.

Table 5 reports on the functional clusters (following categorization of outcome measures; see Methods) that contain all of the most consistent individual outcome measures identified above. Nearly half of the functional clusters that were assessed showed consistent improvement (i.e., >60% consistency) following MPH compared to placebo; these clusters include Divided Attention, Secondary Reaction Time, Sustained Attention, Motor Control, Evoked Potentials, and the following scales: Attention, Oppositional, ADHD, and Impulsivity. The highest consistency was seen for Evoked Potentials, Sustained Attention (Vigilance), and the Oppositional and Attention Scales. The observation-related outcome measures and functional clusters ('scales') were more sensitive at detecting the effects of MPH than task-related measures and clusters. Moreover, executive functioning-related clusters had relatively low improvement ratings.

With respect to evoked potentials, MPH-related changes in outcome measures and/or clusters were evaluated regardless of the direction of change (e.g., positive or negative, increased or decreased). Visual evoked potentials were measured in ten studies[28-37], and late potential amplitudes (≥300 msec) increased in approximately 70% of cases following MPH treatment. In contrast, we found no consistent change in early potentials or evoked potential latencies following MPH treatment. Auditory evoked potentials were measured in three studies[29,30,38] and showed a similar change following MPH treatment.

Dose-response relationships

We next investigated the dose-response relationship of the outcome measures and functional clusters that had a consistent MPH-induced response (>60% consistency). Specifically, we examined the dose-response curve of each outcome that was used in ≥3 studies per dose level (low, medium, or high;

see Methods) or ≥15 studies (Table 6). The outcome measures Go/no-go Task and Scale – ADHD showed reasonably high consistency for all dose levels. The functional cluster Sustained Attention (Vigilance) had a robust dose-response relationship in the medium and high dose levels. The cluster Motor Control also showed an increasing response in the high dose level; in contrast, the low and medium doses gave similar response rates across the studies.

Discussion

The clinical use of methylphenidate (MPH) for treating children with ADHD is currently based on a trial-and-error approach. The availability of MPH efficacy biomarkers may help clinicians determine the optimal type and dose of medication, thus providing the most efficacious treatment regimen. Here, we performed a systematic literature review in order to identify potential biomarkers for assessing the acute effects of a single dose of immediate-release MPH in children and adolescents with ADHD. Using this approach, we expected to identify the most sensitive outcome measures for the effect of MPH, provided that a change in task performance, rating, or observation can be detected after administering a single low dose of MPH; moreover, the responses that were consistently detected in multiple studies should reflect the most robust biomarkers. Outcome measures were clustered into groups of related tests and/or test variants in an attempt to standardize the results across studies and tests, and this was followed by a progressive condensation of results into 20 clusters of related CNS tests. Although 151 different outcome measures were used to assess the effects of MPH, fewer than one-third (47 measures) were used in more than one study. The Continuous Performance Test, Go/no-go Task, and Visual Evoked Potentials, as well as several observation scales – including Following Rules Observations, Oppositional Behavior Observations, On-Task Behavior Observations, and Impulsivity Behavior Observations – were identified as outcome measures that showed a clear, consistent response to therapeutic MPH doses in several studies performed by various research groups. We also observed consistent MPH-induced improvement at the cluster level for Divided Attention, Sustained Attention (Vigilance), Reaction Time, Motor Control, Evoked Potentials, and several scales (Attention, Oppositional, ADHD, and Impulsivity).

In order to be useful in a clinical setting, a biomarker should be sufficiently sensitive to detect the effect of a therapeutic dose of MPH; moreover, a plausible relationship between the biomarker, MPH pharmacology, and/or ADHD pathogenesis should also exist. Several neurotransmitters have been implicated in the pathophysiology of ADHD (and by extension, MPH's mechanism of action). Compelling evidence suggests that dysfunctional dopamine and norepinephrine neurotransmission, as well as dysregulation of dopaminergic pathways, are involved in the pathogenesis of ADHD[39,40]. MPH appears to stimulate the dopaminergic and noradrenergic systems in the fronto-striatal region of the brain, thereby improving symptoms associated with impaired motor and cognitive function. Other neurotransmitters (such as histamine, and serotonin) and nicotine have also been suggested to play a role in the pathophysiology of ADHD[41-45], and both animal and human studies have reported increased levels of these neurotransmitters in the prefrontal cortex following MPH treatment. However, the evidence collected to date does not necessarily support the putative relationship between MPH-induced neurochemical modulation and the clinical improvements observed in ADHD patients following MPH treatment[39,46]. In our study, all of the MPH-sensitive outcome measures – and most of the functional clusters – were associated with the core symptoms of ADHD. Other functional clusters that were previously associated with ADHD pathogenesis and were measured in >5 studies (e.g., working memory, reasoning, and set shifting)[47] failed to show consistent MPH-induced improvements. This finding seems to correspond with the clinical finding that a single therapeutic dose of MPH selectively improves some of ADHD's core features (in particular, attention, impulsivity, and hyperactivity), whereas learning, planning, and organization improve only following chronic MPH treatment (possibly as an indirect consequence of MPH's acute CNS effects). ADHD has also been associated with various deficits in event-related potentials. In the auditory modality,

ADHD-related differences are apparent in all components from the auditory brain-stem response to the late slow wave. Although relatively few studies have investigated the visual attention system, similar differences have been reported for a range of components; for example, the visual P3 component has been reported to differ between children with ADHD and control subjects[48]. Late evoked potentials are associated with stimulus evaluation and matching procedures that are related to attention[37,49]. Our findings show that MPH consistently induces a change in late evoked potential amplitudes.

Previously reported MPH-induced improvements include improvements in impulse control, learning, short-term memory, and activity[10], with the largest improvements in activity level, attention, and inhibition[50]. Pietrzak and colleagues[11] used an approach similar to ours, but their search was limited to cognitive tasks, and they included both non-controlled trials and chronic MPH trials, which may explain the differences between their results and our results. For example, Pietzrak and colleagues reported that saccadic eye movement, planning/cognitive flexibility, attention/vigilance, and inhibitory control were improved by MPH in ≥70% of the studies they reviewed. In contrast, only 50% of the studies they reviewed reported improvements in working memory and divided attention following MPH treatment. In our study, tasks and/or observations that evaluate learning and planning could not be reviewed in our study, as they were not used frequently enough in the studies we reviewed. A recent systematic review and meta-analysis of the effects of MPH on cognitive function[51] found that MPH improves executive and non-executive memory, reaction time, reaction time variability, and response inhibition in children and adolescents with ADHD. In contrast to our study, they included studies with additional non-pharmacological interventions (as long as these interventions were applied to both placebo-controlled randomized study groups); in addition, for studies that included several doses of MPH, they included only the data regarding the highest MPH dose, which may explain their positive findings with respect to memory. Other potentially sensitive biomarkers for MPH effect not included in our database include cognitive performance (sustained attention/vigilance)[52], baseline autonomic arousal (heart rate and blood pressure)[52], and baseline brain activity (EEG theta power)[52], and the contingent negative variation (CNV, a slow negative shift in the EEG that can occurs between a warning signal and an imperative stimulus during a reaction time task)[53].

Ideally, a suitable research biomarker should have a clear dose-response relationship with MPH and should preferably be sensitive to a low therapeutic dose of MPH, criteria that were not addressed in previous reviews. Here, we predefined three discrete dose ranges. The majority of studies in our review used the medium dose range (0.25-0.59 mg/kg), which limited our ability to assess a putative dose-response relationship. The cut-off values for the dose categories were based on clinically relevant ranges. Alternatively, we could have determined the cut-off values based on the distribution of dose levels in our dataset, thereby balancing the number of studies in each dose category. However, this approach would have been *post hoc* (rather than *a priori*) and would not have reflected true clinical practices. In our data set, dose-response relationships were determined for the outcome measures and functional clusters that were sensitive to the effects of MPH in a minimum number of studies. Because our method merely determined the statistical significance of test results following treatment, it did not enable us to detect effect sizes; rather, we could only determine consistency in the measured outcomes across studies. This approach may have masked the identification of a dose-response relationship, particularly for biomarkers that showed a clear response at all dose levels, including the lowest level (for example, with outcome measures from the Go/no-go Task, the functional cluster Motor Control, and outcome measures of the scale ADHD).

Our analysis has several limitations. Firstly, the basic concept of ADHD as a disorder changed several times in terms of both nomenclature and classification in the past few decades. As a result, potentially eligible studies may have been missed. In addition, although differences in the response to MPH have been described between the inattentive/hyperactive and combined subtypes of ADHD[54–56], we did not attempt to differentiate between ADHD subtypes, due in part to an insufficient number of studies. Also, publication bias might

have played a role[57], potentially increasing the publication success of studies that report significant MPH effects. Moreover, although grouping the tests into functional clusters and domains provided a degree of standardization, it also reduced the level of detail with respect to the information collected. Thus, potentially suitable biomarkers might have been missed, given that infrequently used outcome measures were excluded from further analysis.

Other limitations are inherent to the nature of the studies that have been published. Studies with a period of ≥5 half-lives between placebo and MPH occasions were included to ensure complete washout; however, in some studies, the effects of MPH on withdrawal – rather than MPH's effects on the condition itself – may have been measured. In addition, several studies used different criteria for selecting subjects, leading to potential differences in baseline impairment and subsequent differences in the magnitude of the response to treatment. Our search also returned studies in which subjects received prior treatment with MPH. Differences between ADHD patients who were previously treated with MPH and 'MPH-naïve' patients have been reported in networks associated with executive control[58] and dopaminergic metabolism[84], and this difference may have influenced our findings. In addition, several studies used a titration scheme; rather than controlling the MPH dose given before the study period, the children were stabilized with an optimal MPH dose (determined by the treating clinician) before evaluating the effect of the treatment. Patients receiving a high dose of MPH (i.e., 60 mg) have been reported to exhibit smaller changes in clinical measures during placebo treatment, suggesting that patients who require a higher dose of MPH are likely to have a worse outcome if left untreated. These subjects also exhibited higher sensitivity to drug treatment, reflected in smaller estimated EC_{50} values[59], consistent with previous reports that children with more behavior problems at baseline tend to respond better to MPH[9,60,61]. Moreover, the majority of studies included boys 5-13 years of age. Only a few studies (primarily the more recent studies) also included preschoolers and adolescents with ADHD and/or included a reasonable numbers of girls. A limited body of evidence suggests that aside from the preschool period[62,63], few age-related differences exist during childhood and adolescence with respect to the response and tolerance to MPH[64]. Because relatively few published studies specifically examined the moderating effect of gender, and because sample sizes were questionable in some studies, no clear conclusions can be drawn regarding whether gender affects the response to treatment[64,65]. Pietrzak and colleagues[11] reviewed several other factors of influence related to intra-individual and inter-individual differences in medication response, including the study design and repeated neuropsychological assessments. Our dose-response analysis was complicated further by several additional factors. For example, effect profiles can differ among outcome measures, including the effect's time of onset, duration, and time to reach maximal effect. The stimulant-induced reduction in motor activity can persist for up to 7-8 hours, whereas the drug's effects on attention last for only 2-3 hours[39,66]. Because most studies did not include repeated effect measurements, it is conceivable that in some studies the time points of specific measurement did not coincide with the time of maximal effect, thereby missing potentially significant improvements. In addition, previous studies reported evidence of acute tolerance to MPH[67,68]. MPH pharmacokinetics and/or pharmacodynamics also vary among children with ADHD. Thus, it is possible that some studies lacked a sufficiently large sample size to detect a significant effect. Although this might have been overcome by performing a formal quantitative meta-analysis, in nearly all cases this would have been hampered by the lack of uniform quantitative outcome parameters. The change from baseline following MPH treatment can also depend on the individual patient's baseline value (i.e., intrinsic state) and is estimated to account for approximately half of the variability observed in MPH's effects[69].

Nevertheless, despite these limitations, we identified several tests that could potentially serve as biomarkers for monitoring the acute effects of a single dose of MPH-IR in pediatric ADHD. The most reliable tests were related to ADHD's core features of motor control, attention and impulsivity, and event-related potentials. These potential biomarkers might help identify responders versus non-responders following a test dose of MPH. Because dose-effect relationships could not be quantified, these tests and clusters should be

investigated further in order to thoroughly evaluate the dose-response relationships, including effect size and, and establish clinically relevant changes. Our study revealed that these studies would benefit greatly from a certain degree of standardization. Ideally, these studies should include concentration- (in addition to dose-) effect relationships at several time points in order to profile the effect of MPH treatment in children and adolescents with ADHD. Short-term data is generally inadequate for assessing a long-term treatment response, as large-scale studies have shown that short-term response rates – which can be as high as 75-80% – often drop to 55-60% over the long run. Therefore, the predictive value of these candidate MPH biomarkers should be tested in long-term trials. In addition, performing multiple tests – rather than one test – may be preferred in such a long-term trial, as multiple tests can yield a more precise and stronger prediction of the response to MPH treatment and can account for the heterogeneity of ADHD[52]. This research should also include biomarkers for MPH tolerance, as many children who respond positively to MPH also experience adverse side events[70,71], potentially reducing treatment compliance or causing the patient to discontinue treatment altogether[70–72]. Finally, these putative MPH biomarkers could help guide future research regarding the core pathology of ADHD, MPH's mechanism of action, and the effects of stimulant use in children in general, as distinct classes of drugs can elicit distinct effect profiles[12–17].

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TABLE 1 **Literature search queries**

Database	Full search query
PubMed	('Attention Deficit Disorder with Hyperactivity'[Mesh] OR 'attention deficit hyperactivity disorder'[all fields] OR 'attention deficit disorder'[all fields] OR 'adhd'[all fields] OR 'minimal brain disfunction'[all fields] OR 'attention-deficit/hyperactivity disorder'[all fields]) AND ('methylphenidate'[Mesh Terms] OR 'methylphenidate' [All Fields] OR ('methylphenidate'[Mesh Terms] OR 'methylphenidate'[All Fields] OR 'dexmethylphenidate' [All Fields]) OR ('methylphenidate'[Mesh Terms] OR 'methylphenidate'[All Fields] OR 'ritalin'[All Fields]) OR 'stimulant medication'[all fields] OR 'stimulant medications'[all fields]) AND ('humans'[Mesh Terms] AND English[lang] AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Conference[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Evaluation Studies[ptyp] OR Research Support, Non US Gov't[ptyp] OR Research Support, US Gov't, Non PHS[ptyp]))
EMBASE	(*attention deficit disorder/ or attention deficit hyperactivity disorder.ti,ab. or attention deficit disorder. ti,ab. or adhd.ti,ab. or minimal brain disfunction.ti,ab.) AND (methylphenidate.ti,ab. or *methylphenidate/ or dexmethylphenidate.ti,ab. OR Ritalin.ti,ab.) AND (biomarker*.mp. or biological marker/ or biological marker*. mp. OR treatment outcome*.mp. or treatment outcome/ OR Treatment Response*.mp. OR Treatment Effect*. mp. OR predictor*.mp.)
PSYCINFO	(DE 'Attention Deficit Disorder with Hyperactivity' or DE 'Attention Deficit Disorder' or TX ADHD or TX attention deficit disorder or TX attention deficit hyperactivity disorder or TX minimal brain disfunction) AND (DE 'Methylphenidate' OR TX methylphenidate OR TX dexmethylphenidate OR TX Ritalin) AND (DE 'Biological Markers' OR TX biological marker* OR TX biomarker* OR DE 'Treatment Outcomes' or TX treatment outcome* or TX treatment response* OR TX treatment effect* OR TX predictor*

TABLE 2 **Characteristics of studies included in the analysis**

		Tests n (%)	Observations n (%)	Total n (%)
Number of studies		72	31	78
Sex	Male	1769 (91%)	1423 (93%)	2695 (92%)
	Female	168 (9%)	100 (7%)	234 (8%)
MPH dose	High (≥0.60 mg/kg)	26 (36%)	12 (39%)	29 (37%)
	Medium (0.25-0.59 mg/kg)	66 (92%)	28 (90%)	72 (92%)
	Low (0.1-0.25)	15 (21%)	6 (19)	16 (21%)
Wash-out period	> 1 week	9 (13%	0 (0%)	9 (12%
	> 5 half-lives	63 (88%)	31 (100%)	69 (89%)
Age	5-13 years	58 (81%)	27 (87%)	64 (82%)
	<5 or > 13 years	14 (19%)	4 (13%)	14 (18%)
Design	Crossover	66 (92%)	29 (61%)	72 (92%)
	Parallel Group	6 (8%)	2 (7%)	6 (8%)

TABLE 3 Reported test, observation per cluster, and domain

Domain	Cluster	Standardized Names of Tests and Observations	Number of tests (n)	Number of studies (n)
		TESTS	533	
Attention			148	72
	Divided Attention	Arrow/Sound (In)CompatibilityTask, Dichotic Listening Task, Divided Attention Task, Dual Task	7	5
	Focused/Selective Attention	Alertness Task, Arrow/Direction (In)Compatibility Task, Auditory Selective Attention Task (ERP), Children's Checking Task, Find-A-Word Task (nonsense word), (Go/No-)Go Task, Graduated Holes Task (*), Letter Matching Task, Letter Search Task, Matching Familiar Figures Task, Matching to Sample Task (simultaneous), Oddball Task (ERP), Operant Task, Orientation Task (ERP), Puzzle Task, Saccadic eye movements - predictable location/timing, Selective Auditory Attention Task, Stroop Word Color Task, Tachistoscopic Task, Visual Memory Search Task, Visual Scanning Task, Visual Selective Attention Task (ERP), Visual Spatial Focused Attention Task (ERP)	54	27
	Reaction Time	Eriksen Flanker Task (*), Choice Reaction Time Task, Flexibility Task(*), Go/No-Go Task, Oddball Task (*), Reaction Time Task, Saccadic eye movements - visually guided (*), Set Shifting Task (*), Stroop Word Color Task (*)	37	15
	Sustained Attention (Vigilance)	Academic Task Performance, Arithmetic Task, Eriksen Flanker Task (ERP), Auditory Selective Attention Task, Card Sorting Task, Change Task, Continuous Performance Task (ERP), Find-A-Word Task - common words, Find-A-Word Task - nonsense word, Easy/Hard Decision Task (ERP), Letter Matching Task, Oddball Task, Puzzle Task*, Set Shifting Task*, Timed Reading Task*, Vigilance Task, Visual Selective Attention Task, Word discovery Task	50	25
Behavior			2	1
	Aggression	Social Information Processing	2	1
Executive			243	66
	Creativity	Alternate Uses Test, Narrative Discourse/Task*	4	2
	Impulsivity	Arrow/Direction (In)Compatibility Task*, Arrow/Sound (In)CompatibilityTask*, Auditory Selective Attention Task*, Cambridge Gamble Task, Change Task, Circle Tracing Task, Continuous Performance Task*, Divided Attention Task*, Eriksen Flanker Task, Follow Task, Go/No-Go Task (ERP), Information Sampling Task, Matching Familiar Figures Task*, Oddball Task*, Operant Task*, Orientation Task*, Reaction Time Task*, Saccadic eye movements - anti saccade, Set Shifting Task, Stroop Word Color Task, Tower of London Task*, Vigilance Task*, Visual Scanning Task*, Visual Selective Attention Task*, Visual Selective Attention Task*, Visual Spatial Focused Attention Task*	86	29
	Motivation	Find-A-Word Task - nonsense word, Persuasive Persistence Task	5	2
	Planning	Stockings of Cambridge, Tower of London Task	6	3
	Reasoning/ Association/ Problem Solving	Academic Task Performance, Arithmetic Task, Classroom Observation, Listening Comprehension Task, Narrative Discourse/ Task*, Spelling Task, Story Retelling Task	42	12
Executive	Set Shifting	Alternate Uses Test, Card Sorting Task, Change Task, Flexibility Task, Set Shifting Task	14	7
	Spatial Orientation	Visual Spatial Processing Task	1	1
	Time/Distance Estimation	Sensorimotor Anticipation Task, Time Discrimination Task	2	1
	Working Memory/ Immediate Recognition	Arithmetic Task (mental), Digit Span - Backward, Digit Span - Forward, Dual Task*, Matching to Sample Task (delayed), Pattern Recognition Task, Spatial Recognition Memory Task, Spatial Span - Backward, Spatial Span - Forward, Spatial Span Task, Spatial Working Memory Task, Spatial Working Memory Task - Backward, Spatial Working Memory Task - Forward	83	9
Language			39	16
	Comprehension	Listening Comprehension Task, Reading Comprehension Task, Story Retelling Task	6	3
	Production	Alternate Uses Test, Digit Naming Task, Instances test, Letter Naming Task, Naming Task, Narrative Discourse/ Task, Rhyming Task, Story Retelling Task, Word discovery Task	18	6
	Spelling/Grammar/ Semantics	Color Naming Task, Mother-Child Language, Sequence Insertion Task, Spelling Task, Tachistoscopic Task, Timed Reading Task, Trigram Naming Task	15	7
Memory			27	14
	Auditory/Verbal Memory: Delayed Recall	Paired Associate Learning Task, Spelling Task	5	2
	Auditory/Verbal Memory: Delayed Recognition	Listening Comprehension Task, Verbal Memory Task	4	2
	Auditory/ Verbal Memory: Immediate Recall	Letter Matching Task*, Social Information Processing, Story Retelling Task, Verbal Memory Task	8	4
	Learning	Paired Associate Learning Task, Spelling Task	8	4
	Visual/Spatial Memory: Delayed Recognition	Visual Memory Task	1	1
	Visual/Spatial Memory: Immediate Recall	Visual Memory Task	1	1
Motor			42	11
	Postural Stability	Postural Stability Task	1	1
	Motor Control	Activity level, Finger Tapping, Graduated Holes Task, Softball Performance (sports), Usual Walking Task	32	8
	Visuo-Motor Control	Pointing Task, Visual Motor Integration Task	9	2

Perception			3	1
	Visual Perception	Tachistoscopic Task	3	1
Neurophysiologic			32	14
	EEG	EEG - CPT, EEG - eyes open	8	2
	Evoked Potential	Auditory Evoked Potential, Visual Evoked Potential	23	11
	Eye Movements - Saccadic	Saccadic eye movements - visually guided/(anti)saccadic mixed	1	1
	MEG	Magnetoencephalography	1	1
Subjective Experience			2	1
	Empathy	Story Retelling Task	2	1
(Neuro) Endocrine			2	2
	Prolactin	Prolactin determination	1	1
	Serotonin	5-HIAA determination	1	1
		OBSERVATIONS	232	69
Attention			30	13
	Scale - Attention	ADD-h Comprehensive Teacher Rating Scale (ACTeRS) (P), Classroom Observation (R), On-task Behavior Observation (R/T), Profile of Mood States (S), Softball Performance (sports) (R), Swanson, Nolan and Pelham Questionnaire (SNAP-IV) (P), VAS Alertness (S)	30	13
Behavior			59	14
	Scale - Aggression	Oppositional Behavior Observation (R), Profile of Mood States (S)	4	2
	Scale - Anxiety	Profile of Mood States (S)	2	1
	Scale - Compulsive/ Obsessive	Clinical symptoms of perseveration (R)	4	1
	Scale - Oppositional	Behavior after Failure (R/S); Behavior after Success (R/S); Conners, Loney and Milich Scale (CLAM) (T); Daily Report Card System (R); Following Rules Observation (R/T); IOWA Conners Rating Scale (R); IOWA Conners Teachers Rating Scale (T); Oppositional Behavior Observations (R/T)	49	10

Disease Intensity			41	9
	Scale - ADHD	Abbreviated Conners Teacher Rating Scale (T), Behavior Evaluation (S), Behavior Observation (R), Conners Global Index (R), Conners, Loney and Milich Scale (CLAM) (T), Daily Report Card System (R), IOWA Conners Rating Scale (R), IOWA Conners Teachers Rating Scale (T), UC-Conners Child Behavior Scale (R)	41	9
Executive			41	12
	Scale - Impulsivity	ADD-h Comprehensive Teacher Rating Scale (ACTeRS) (P), Clinical Symptoms of Perseveration (R), Conners Revised Teacher Rating Scale (T), Conners Revised Teacher Rating Scale (T), Impulsivity Behavior Observation (R), Swanson, Nolan and Pelham Questionnaire (SNAP-IV) (P)	33	9
	Scale - Motivation	Behavior after Failure (S/R), Behavior after Success (S/R), Effort Rating (R), Math Cheating Task (R), Success/Failure Puzzle Task (R)	8	3
Social behavior			32	8
	Scale - Social Interaction	Social Behavior Observation (R/T), Social Information Processing (S/R)	32	8
Subjective Experience			29	13
	Scale - Calmness	VAS Calmness (S)	1	1
	Scale - Confusion	Profile of Mood States (S)	2	1
	Scale - Fatigue	Profile of Mood States (S)	2	1
	Scale - Mood	Mood Evaluation (S), Profile of Mood States (S), UC-Conners Child Behavior Scale (R), VAS Happiness (S)	8	4
	Scale - Performance	Behavior after Failure (S), Behavior after Success (S), Performance Prediction (S), Self-Evaluation (S), Success/Failure Puzzle Task (S)	10	4
	Scale - Drug Effect	Attribution Evaluation (S), Success/Failure Puzzle Task (S)	6	2

(ERP), indicates tasks that were used to measure the effect of MPH on attention of impulsivity using ERP.
Subjective measure could be rated by a Researcher (R), a teacher (T), a Parent (P) or the subject (S).
*, indicates a secondary parameter of the task.

TABLE 4 Improvement following MPH for each individual test or observation that was used in at least five studies

	Test/Observation	Number of tests with improvement (n)	Total of tests (n)	Impro-vement (% of tests)	Studies (n)
Test	Go Task	7	11	63.6	7
	Reaction Time Task	9	18	50.0	6
	Continuous Performance Task	16	21	76.2	9
	Go/No-Go Task	13	21	61.9	10
	Arithmetic Task	11	28	39.3	6
	Visual Evoked Potential	16	19	84.2	10
Observation	Following Rules Observation	15	15	100.0	5
	Oppositional Behavior Observations	12	14	85.7	6
	On-task Behavior Observation	12	12	100.0	7
	Impulsivity Behavior Observation	13	19	68.4	6
	Social Behavior Observation	12	32	37.5	6

TABLE 5 Effect of MPH for each functional cluster that was used across at least five studies

Domain	Cluster	Test/ Observation	Improvement (%)			Tests (n)	Studies (n)
			(-)	(=)	(+)		
Attention	Divided Attention	Test	-	28.6	71.4	7	5
	Focused/Selective Attention	Test	1.9	54.7	43.4	54	26
	Reaction Time	Test	-	50.0	50.0	28	9
	Reaction Time*	Test*	-	25.0	75.0	8	6
	Sustained Attention (Vigilance)	ERP	-	60.0	40.0	10	6
	Sustained Attention (Vigilance)	Test	-	23.9	76.1	50	22
	Scale - Attention	Observation	-	16.7	83.3	30	13
Behavior	Scale - Oppositional	Observation	2.0	12.2	85.7	49	10
Disease Intensity	Scale - ADHD	Observation	-	19.5	80.5	41	9
Executive	Impulsivity	Test	-	50.0	50.0	46	16
	Impulsivity*	Test*	-	43.6	56.4	39	13
	Reasoning/Association/ Problem Solving	Test	-	61.0	39.0	41	11
	Set Shifting	Test	-	57.1	42.9	14	7
	Working Memory/ Immediate Recognition	Test	-	69.5	30.5	82	8
Language	Production	Test	-	83.3	16.7	18	6
	Spelling/Grammar/ Semantics	Test	6.7	46.7	46.7	15	7
	Scale - Impulsivity	Observation	-	21.2	78.8	33	9
Motor	Motor Control	Test	-	28.1	71.9	32	8
Neuro-physiologic	Evoked Potential	Test	-	13.0	87.0	23	11
Social behavior	Scale - Social Interaction	Observation	-	64.9	35.1	32	8

'+' reflects an improvement or increase, '=' reflects no significant effect and '-' reflects an impairment or decrease as measured by the corresponding test. Whenever tests provided different parameters with information on more than one functional domain, effects were scored separately, and the secondary effects were marked (*).

TABLE 6 **Dose-response relationship for outcome measures and functional clusters that showed a consistent MPH response in a reasonable number of studies**

Domain, cluster and/or test	Test/ Observation	Low Dose				Medium Dose				High Dose			
		(-)	(=)	(+)	n	(-)	(=)	(+)	n	(-)	(=)	(+)	n
Attention													
Sustained Attention (Vigilance)	Test	-	100	0	2	-	28	72	22	-	11	89	6
Motor													
Motor Control	Test	-	33	67	5	-	33	67	5	-	18	82	3
Disease Intensity													
Scale - ADHD	Observation	-	11	89	4	-	27	73	9	-	0	100	4
Individual test													
Go/No-go Task	Test	-	20	80	5	-	50	50	6	-	25	75	3

n is the number of studies in which the cluster was evaluated (for each dose)