Therapeutic Response to Methylphenidate in Children with ADHD: Effect of Observer/Setting and Gender of the Observer

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Abstract (English)

Background: The diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), the most commonly diagnosed psychiatric disorder in children, requires a clinical synthesis of information obtained from various sources including parents and teachers. Further, titration of stimulant medications, the first line pharmacological treatments for ADHD, is a feedback loop dependent on these longitudinal observations. The validity of this feedback loop is dependent on characterization of therapeutic response (TR) and side-effects (SE) observed in various settings (school, home) and along several dimensions (clinical, neuropsychological) and its interactions with pertinent variables such as gender. On these questions, sparse and often conflicting information is currently available from rigorous randomized controlled trials (RCT). Existing literature in ADHD and similar studies from other domains made us hypothesize that TR would vary as a function of the observer but retain enough commonality to suggest overall positive improvement with stimulant medications. We also hypothesized that gender of the observer may be relevant to the behavioural assessment of ADHD relevant behaviours and response to medication.

Objectives: This project aimed to answer two key questions relating to *TR observed with MPH and Placebo*:
1. What is the *role of observation setting* (parent, teacher, classroom simulated situation-RASS, neuropsychological-CPT Overall Index, clinical staff)?
2. What is the *role of the gender of the child and the observer* (parent, teacher)?

Methods: The ADHD Pharmaco-behavioral study is an ongoing study at the Douglas Hospital in Montreal. Following a one week washout period, children with ADHD undergo a two week double-blind, randomized, cross-over clinical trial with Methylphenidate (MPH) and placebo. Clinical information (Conner's Global Index) on therapeutic response is obtained from teachers (CON-T) and parents (CON-P) at baseline and during the two weeks of the clinical trial. Side effect rating scales were completed by parents during the two-week trial. Children also participate in the classroom-simulated test, the Restricted Academic Activity Scale (RASS), and neuropsychological tests including the Conner's Performance Test (CPT), which is repeated

during the two weeks. Assessment is done by trained observers to arrive at a clinical global impression of improvement (CGI-I) during the two weeks. Finally, a group consensus of response to treatment taking into account all the available information (GIP) and prior to the blind being broken is made on the basis of improvement relative to the baseline state.

The difference scores between the treatment and placebo weeks were calculated for all the measures. Following examination of the distribution of demographic variables, Pearson's correlation was performed to examine the correlation of behavioral changes across observation settings, independent sample t-tests were carried out to examine the role of gender. Appropriate bootstrap, non-parametric methods, and covariates were used based on the data distribution and side-effects to MPH.

Results: 526 children with ADHD are included in the present thesis. CON-T was obtained from 81 male teachers and 445 female teachers, CON-P was obtained from 441 female parents and 65 male parents. Demographic distribution of variables was in line with previous population estimates and significant overall TR is noted with MPH in all observation settings. For the first question based on observer setting, baseline scores by parents and teachers are significantly correlated for Restless-Impulsive (RI), Emotional-Labile (EL) dimensions of the Conners'Index scores and with CPT Overall Index baseline scores. Therapeutic response correlations are seen mainly with regard to the RI dimension. The CPT Overall Index, RASS, CGI-I, GIP show significant correlations among them, but are not correlated with parent and teacher assessments.

For the second question based on gender, significant interactions between child's gender and teacher's gender on CON-T scores at baseline and on treatment response were noted. Only main effects of child's gender and parent's gender at baseline were noted on the CON-P. No significant gender differences were seen in CPT Overall Index, RASS, CGI-I, GIP with treatment.

Conclusion: Significant treatment response is noted with MPH in all observation settings. Parents and teachers have significantly correlated baseline assessments and their evaluations correlate with CPT Overall Index baseline assessment. However, parents and teachers'

assessments of TR correlate poorly and do not correlate with other neuropsychological and clinical assessments of treatment response, suggesting significant heterogeneity. Teachers' and parents' gender interact with the child's gender in how symptoms at baseline and treatment responses are evaluated.

These observations suggest that the child's behaviour, particularly response to treatment, could differ depending on the environment with complex interactions between the environment and treatment. Alternatively, but not exclusively, these results may suggest that parents and teachers could have differences in evaluation criteria at baseline and for TR. The studies strongly support the clinical paradigm of synthesizing information from many observers in ADHD management. Future studies need to examine the reasons for the differences observed in this study.

Résumé (Français)

Contexte: Le diagnostic du trouble déficitaire de l'attention avec hyperactivité (TDAH), le trouble psychiatrique le plus fréquemment diagnostiqué chez les enfants, nécessite une synthèse de l'information obtenue à partir de diverses sources, y compris les parents et les enseignants. De plus, l'ajustement de la dose des médicaments stimulants, représentant la première ligne de traitement pharmacologique pour le TDAH, est une boucle de rétroaction guidée par ces observations longitudinales. La validité de cette boucle de rétroaction dépend de la caractérisation de la réponse thérapeutique (TR) observés dans différents contextes (enseignant, parent, neuropsychologique, clinique) et ces interactions avec des variables pertinentes telles que le genre. Sur ces questions, les publications basées sur des essais contrôlés randomisés rigoureux (ECR) sont rares et souvent contradictoires. Sur la base de la littérature existante nous avons émis l'hypothèse que TR varieraient en fonction de l'observateur mais conserveraient suffisamment de points communs pour suggérer une amélioration globale positive avec des médicaments stimulants. Sur la base de la littérature dans d'autres domaines, nous avons également émis l'hypothèse que les différences fondées sur le genre de l'observateur pourrait être pertinents a l'évaluation des comportements reliés au TDAH et à la réponse aux médicaments.

Objectifs: Ce projet vise à répondre à deux questions clés relatives à TR observées avec MPH et Placebo:
1. Quel est le rôle de l'observateur et le milieu de l'observation (parent, enseignant, situation simulée en classe - RASS, l'indexe CPT neuropsychologique, personnel clinique)?
2. Quel est le rôle du genre de l'enfant et de l'observateur (parent, enseignant)?

Méthodes: L'étude Pharmaco-comportementale et génétique du TDAH est une étude en cours à l'Hôpital Douglas à Montréal. Après une période sans médication d'une semaine, les enfants atteints de TDAH participent à un essai clinique en double-aveugle randomisé de deux semaines avec du méthylphénidate (MPH) et du placebo. L'information clinique (Conner's Global Index) sur la réponse thérapeutique est obtenue auprès des enseignants (CON-T) et des parents (CON-P) pendant l'évaluation de base et pendant les deux semaines de l'essai clinique. Les échelles d'évaluation des effets secondaires ont été complétées par les parents pendant l'essai de deux

semaines. Les enfants participent également aux tests simulées en classe, l'Échelle d'activité académique restreinte (RASS) et les tests neuropsychologiques, y compris le test de performance de Conner (CPT) qui se répètent au cours des deux semaines. L'évaluation au laboratoire est faite par des observateurs formés pour compléter une échelle clinique d'impression globale d'amélioration (CGI-I) au cours des deux semaines. Enfin, une discussion de groupe dirigé par le clinicien parvient à un consensus de réponse à la thérapie en tenant compte de toutes les informations disponibles (GIP) et avant que l'aveugle soient levé. Ce consensus est fait basé sur une amélioration relative à la semaine de base.

Les scores de différence entre les semaines de traitement par methylphenidate et placebo ont été calculés pour toutes les mesures. Après examen de la distribution des variables démographiques, des corrélations de Pearson ont été effectuées pour examiner le rôle du milieu d'observation, des tests d'échantillon indépendants ont été effectués pour examiner le rôle du genre. L'amorçage approprié, les méthodes non-paramétriques et les covariables ont été utilisés en fonction de la distribution des données et des effets secondaires sur MPH.

Résultats: 526 enfants atteints de TDAH sont inclus dans la thèse présente, CON-T a été obtenu auprès de 81 enseignants et 445 enseignantes, CON-P a été obtenu auprès de 441 mères et 65 pères. Les variables démographiques étaient conformes aux estimations précédemment rapportées dans la littérature et le TR global significatif est noté avec MPH selon tous les paramètres d'observation. Pour la première question basée sur l'effet de l'observateur, les scores de base des parents et des enseignants sont significativement corrélés pour les dimensions trémoussant-impulsif (RI) et émotif-labile (EL) de l'indexe Conners' et les scores de référence du CPT « Overall Index ». Les corrélations de réponse thérapeutique sont observées chez les garçons ayant le sous-type RI. Le CPT « Overall Index », RASS, CGI-I, et GIP présentent des corrélations significatives entre elles, mais ne sont pas corrélés avec les évaluations des parents et enseignants.

Pour la deuxième question explorant l'effet du genre, des interactions significatives entre le genre de l'enfant et le genre de l'enseignant sur les scores CON-T à la base et pour le traitement ont été notées. Seuls les effets principaux du genre de l'enfant et du genre des parents au cours de

l’évaluation de base ont été notés sur le CON-P. Aucune différence significative entre les sexes n'a été observée pour CPT « Overall Index », RASS, CGI-I, ou G IP avec traitement.

Conclusion: Une réponse significative au traitement est notée avec MPH dans tous les environnements d'observation. Les parents et les enseignants ont des évaluations de base corrélés et sont en corrélation avec les évaluations de base du CPT « Overall Index ». Cependant, les évaluations des parents et des enseignants varient selon la TR et ne sont pas en corrélation avec d'autres évaluations neuropsychologiques et cliniques s de la réponse au traitement suggérant une hétérogénéité significative. Les genres des enseignants et parents interagissent avec le genre de l’enfant en ce qui concerne l’évaluation de symptômes à la base et après le traitement.

Ces observations suggèrent que le comportement de l'enfant, particulièrement la réponse thérapeutique, pourrait varier en fonction de l'environnement avec des interactions complexes entre l'environnement et le traitement. Alternativement, mais pas exclusivement, ces résultats pourraient suggérer que les parents et les enseignants pourraient avoir des différences dans les critères d'évaluation au cours de l’évaluation de base et pour la TR. Ces études appuient fortement le paradigme clinique de synthèse d'informations provenant de nombreux observateurs dans la gestion du TDAH. Les études futures doivent examiner les raisons pour les différences observées dans cette étude.

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I wish to convey my sincere appreciation and deep gratitude to my supervisor Dr. Ridha Joober for his support, guidance and encouragement throughout my training. I have been greatly inspired by his critical and insightful approach to research in psychiatry, humane approach towards empowering subjects who struggle with mental health, and the care and dedication bestowed on every member of his team. He is a role model in many ways to all members of the ADHD team.

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Most of all, I am eternally grateful to my wife, Dr. Mamatha Bhat whose affection and presence makes everything possible and worthwhile. Many thanks to our toddlers Manish Bhat & Sachin Bhat whose every hug reminds us that joy and meaning are truly in the eyes of the observer.

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Preface and Contribution of Authors:

This manuscript-based thesis examines the role of setting/observer (school vs home vs clinic), gender (male vs female) of both the patient and the observer, on therapeutic response observed with stimulant medication in children with ADHD. It begins with an introduction to the variables of interest that can impact on ADHD clinical assessment and sets the stage for our two questions of interest to be explored in two successive manuscripts. This is followed by the two manuscripts that are linked by transition pages to provide closure and transition to the subsequent question of interest. The conclusion summarizes observations from the two studies, the limitations of the studies, and questions raised for future studies. Finally, a glossary provides a quick summary of keywords used in the thesis.

Under the guidance of Dr. Joober, Venkat Bhat conceptualized and elaborated on the research questions, worked with the ADHD team to appreciate and clarify details pertinent to the research question, analyzed the data, interpreted the results, prepared the manuscripts and formatted them into a manuscript-based thesis.

Ridha Joober as the project supervisor and co-lead of the ADHD team, was key to the critical appreciation of underlying concepts, informed data analysis, ensured correct interpretation of results and packaging them all into meaningful manuscripts.

Natalie Grizenko as co-lead of the ADHD team and as a member of the thesis advisory committee was instrumental in providing an appreciation for the clinical data, helpful feedback and supervision.

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Overview (Overall Rationale and Objectives of this Research)

ADHD is the most commonly diagnosed disorder of childhood and stimulant medications such as Methylphenidate (MPH) are the mainstay of pharmacological management of ADHD. ADHD diagnosis, the initial choice of stimulant medications and titration to achieve optimal outcomes is based on a collaborative synthesis of information obtained by the clinician from multiple sources including information from teachers, parents, and direct clinical observations. While these different observers could converge on observing therapeutic response (TR) in some dimensions, they could also tap into some non-overlapping areas of TR, which could underline heterogeneity in TR. Variables related to treatment, such as side effects (SE) induced by MPH, and variables related to the disorder, such as gender, could also contribute further to the heterogeneity in TR.

Clinical diagnosis of ADHD has traditionally emphasized obtaining information from multiple sources. However, less emphasis has been put on delineating the sources of heterogeneity in defining treatment response taking into account the perspectives of the different observers. A better understanding of the heterogeneity in TR would be essential to have more precision in treatment titration and to achieve optimal outcomes for children with ADHD.
However, perspectives of the observers of TR and role of pertinent variables such as gender have not been previously compared and contrasted simultaneously using a rigorous RCT paradigm.

Based on the ongoing pharmaco-behavioral study in children with ADHD at the Douglas Institute, this project aimed to answer two key questions relating to variation of *TR observed with MPH* as a function of clinically important parameters:

1. What is the *role of observation setting* (home, school, laboratory) and observers (parent, teacher, clinical staff)?
2. What is the *role of the gender of the child and the observer* (parent, teacher)?

Therapeutic Response in Children with ADHD: What is The Role of Observation Setting?

The first manuscript examines perspectives that relate to the "eye of the observer" in the assessment of TR with MPH. In the context of a two-week double-blind, randomized, cross-over clinical trial with Methylphenidate (MPH) and placebo, we examined several observers/observation settings. We hypothesized that there would be heterogeneity in TR based on the observer, which would include commonality and differences.

526 children (420-male, 106-female; average age 8.9±1.8) were evaluated by 81 male teachers, 445 female teachers; 441 female parents and 65 male parents. As expected, a significant overall improvement was noted in all observation settings with MPH as compared to placebo ($P<0.00$). The significant side-effects with MPH, as evaluated by parents, were insomnia, talking less, decreased appetite, stomachaches and headaches, and an increase in pulse (2 BPM) and Diastolic Blood Pressure (2 mm Hg). The evaluations by parents, teachers and the CPT Overall Index test showed significant correlations with each other at baseline but a different pattern was noted with regard to response to MPH. Indeed, the correlation between teacher and parent evaluations of TR was limited to the RI dimension of the Conners' Global Index. Further, CPT Overall Index, RASS, CGI-I showed significant correlations among themselves but did not show significant correlations with TR as assessed by teachers and parents. The group impression of improvement (GPI) that took into consideration all available information showed significant correlations with scores obtained from all the other observers. The effect sizes of the observed correlations were small for CON-T/CON-P ($r = 0.2$ for baseline; $r = 0.1$ for TR), medium for classroom simulated situations and all the other laboratory based measures ($r = 0.3$ for CPT/RASS; 0.4 with CGI-I/RASS), and large for GPI ($r = 0.5$/RASS)

The results supported our hypothesis of heterogeneity in multiple ways. The commonalities among the observers were that children demonstrate an overall improvement with MPH and that baseline evaluations show correlations among all observers. However, with regard to TR, only the neuropsychological evaluations, the classroom simulated situations, and the CGI-I showed commonalities, and these measures are not correlated with teacher/parent assessments. Importantly, the commonalities had a small effect size. These results, pointing towards sources

of heterogeneity, particularly with TR, reiterate the traditional clinical approach of medication titration based on the synthesis of multiple observations. This was demonstrated, in part, by the greater commonality of GPI with all scores and the largest effect size seen with GPI.

Manuscript 1

Therapeutic Response in Children with ADHD: Role of Observers/Setting

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Abstract

***Objectives*:** Information obtained from parents and teachers is used to initiate stimulant treatments and for further titration to achieve optimal therapeutic response (TR) in ADHD. Thus, it is important to delineate the characteristics of TR observed by parents and teachers when children with ADHD are on stimulant medications, and put this information in the context of simultaneously obtained clinical information based on direct observation of the child behaviors. This study aims to examine TR obtained in various observation settings (home, school, clinic) by different observers (parents, teachers, clinicians), and characterize the extent of correlation in these observation settings at baseline and with regard to treatment response (TR). SE observed by parents are examined for their impact on TR obtained from the various observation settings. We hypothesized that there would be heterogeneity in TR with commonalities and differences among observers of TR.

Methods: Children with ADHD underwent a two-week double-blind, randomized, cross-over clinical trial with Methylphenidate (MPH) and placebo, and information was obtained from various sources during each week. This includes the Conner's Global Index from parents (CON-P), teachers (CON-T), the clinical global impression for improvement assessed by clinicians (CGI-I), and direct observations of child behaviors in a very structured classroom-like environment (Restricted Academic Situation School, or RASS), and cognitive tests evaluating sustained attention (CPT Overall Index). In addition, all available information was assessed to arrive at a consensus score for group impression of improvement (GPI). The difference scores between MPH and placebo weeks were calculated for all variables of interest to obtain measures of treatment response with MPH for each child (TR). Interrelationships of TR in the various observation settings were examined using Pearson's Correlation coefficients. Similarly, side effects were examined using repeated measures ANOVA. Significant side-effects and other pertinent variables were used as covariates using a bivariate partial correlation analysis of TR interrelationship in the various observation settings.

Results: Results from 526 children (420-male, 106-female) with ADHD was included in this study. Statistically significant TR was observed for all outcome variables ($p<0.00$). Insomnia,

talking less, decreased appetite, stomachaches and headaches were the SE noted with MPH (all p-values<0.05), and they were used as covariates in the bivariate correlation analysis. Assessments in all settings and by different observers showed significant correlations at baseline ($p < 0.00$). For TR, a weaker correlation between CON-T and CON-P was observed, and was specific to the Restless/Impulsive dimension of CON-T and CON-P. No significant correlations between CON-T and CON-P on the one hand and CPT Overall Index, RASS and CGI-I on the other hand were observed for TR. However, TR as measured by CPT Overall Index, RASS, CGI-I scores were significantly correlated with each other (all p values <0.00) and TR as measured by the consensus score derived from all the information (GPI) was significantly correlated with all TR outcomes (all p-values <0.00), and showed robust effect sizes.

Conclusion: Treatment response to methylphenidate is a complex phenotype. Here, we show that although TR is consistently observed in all observation settings supporting the very well established efficacy of MPH in ADHD, there are considerable variations in TR that are contingent on the observers/settings and the specific behaviors that are evaluated. TR between different observers shows a variable correlation between parents and teachers, and no correlation is seen between parents/teacher evaluation of TR on the one hand and CPT/RASS and CGI-I on the other hand. However, TR as measured by CPT Overall Index, RASS and CGI-I showed significantly stronger pair-wise correlations, suggesting common elements in improvements that are not necessarily captured by clinical observations. The results firmly support the need to synthesize information from many sources and is well illustrated by the significant and robust correlation between TR as measured by the GPI and all other dimensions of TR.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed psychiatric disorder in childhood, and stimulant medications are the mainstay of pharmacological treatment in ADHD.[1] Stimulants such as Methylphenidate (MPH) have been demonstrated in clinical trials to reduce inattention and hyperactivity and enhance educational outcomes in children with ADHD.[2] The diagnosis and management of ADHD by clinicians is based on information obtained from parents and teachers, from clinical interviews, and when available from direct measures of the child behavior such as the Continuous Performance Task (CPT) and the Restricted Academic Situation Scale (RASS).[2-6] This information, along with feedback from parents and teachers, is used to begin stimulant treatments, and for further titration to achieve optimal therapeutic response (TR) and minimal side effects (SE).[3,7]

Informant discrepancies have been one of the most robust findings in the childhood psychopathology literature with low concordance among various informant dyads (parent-teacher, teacher-child, parent-child, parent-parent, etc).[8-10] ADHD has a very heterogeneous clinical presentation which is further complicated by the common co-occurrence of comorbidities.[11] Features of ADHD vary based on various demographic features such as gender, socioeconomic status and prenatal life circumstances. In addition, clinical features of ADHD vary across the lifespan. Further, family members of children with ADHD often have a higher prevalence of ADHD themselves due to the high heritability associated with ADHD. This family loading of illness can further contribute to the diverse ADHD clinical phenotype. Traditionally, and in part to make a diagnosis in the context of extensive heterogeneity, there is emphasis on synthesis of information obtained from multiple sources as the children are observed in different contexts.[3,12]

The ADHD clinical phenotype has been extensively studied to characterize heterogeneity,[13] while the treatment response (TR) phenotype with stimulant medications has been less explored from the perspective of heterogeneity. When there is good TR, parents appear to confirm at a higher probability the TR observed by teachers, rather than vice versa.[14] However, in the absence of response neither observer was found to confirm the others' findings.[14] While diagnostic

heterogeneity could contribute to heterogeneity in TR and SE, there could be features that are unique to TR and SE that are independent of the clinical phenotype. Indeed, stimulant medications such as MPH have a good effect size but these medications require titrations tailored to the individual subject to achieve maximal TR and minimal SE. While much of the heterogeneity could be due to factors intrinsic to the child (biological, such as pharmacodynamic and pharmacokinetic, and psychological characteristics), they could also arise from an interplay of factors intrinsic to the observer and to the child.[15] Thus, it is important to unpack this interplay of factors to appreciate observer perspectives on TR observed with MPH.

The TR with MPH appears to be an overall gestalt among various observers of children with MPH. This means that there would be commonalities in the TR phenotype among observers but also that there could be differences. However, the extent of correlation among various observers of TR with MPH has not been previously investigated comprehensively. Importantly, the correlation among various observers/settings of TR (parents, teachers, CPT Overall Index, RASS, clinical) for MPH in ADHD remains poorly characterized. Finally, the role of the most commonly observed SE with MPH in moderating the correlation among various observers has not been explored. A genuine appreciation of the dynamic factors at play can have a positive impact on appreciating sources of heterogeneity intrinsic and extrinsic to the child. This can be of significant help to the clinician in gauging TR and SE, and tailoring treatment recommendations to achieve optimal outcomes for children with ADHD.

This paper aims to examine TR obtained in various observation settings (house, school, laboratory) and by different observers (parent, teacher, clinician), characterize the extent and nature of correlation in these observations with an emphasis on baseline levels of symptoms and TR of these symptoms to Methylphenidate. Similarly, SE observed by parents will be examined during treatment, and for their impact on information obtained from the various observation settings. We expect that consistent TR would be noted in all observation settings. However, we also expect that there would be differences in correlation among the various settings

Methods

Subjects

The ADHD Pharmaco-behavioral study is an ongoing study at the Douglas Mental Health Research Institute in Montreal funded by the Canadian Institutes of Health Research. The current study included a subset of all the subjects in this ongoing study as all the required measures were not available on all subjects. The protocol for the research study was approved by the Research Ethics Board of the Douglas Mental Health University Institute (DMHUI). Children are referred to the DMHUI by family doctors, teachers, community social workers, and pediatricians. These children are evaluated at the Disruptive Behavior Disorders Program and pediatric outpatient clinics of the DMHUI. Children diagnosed at these clinics with ADHD between the ages of 6 and 12 are recruited to the study. Following a detailed explanation of the study, parents provide written consent. Similarly, children gave their assent to participate in the study. More than ninety percent of the children invited to participate in the study by research assistants agreed to participate.

The clinical diagnosis of ADHD is made by experienced child psychiatrists. The diagnosis is based on DSM-IV criteria[16], dependent on clinical interviews of the child and requires the information provided to the clinician from at least one parent at the time of the clinical interview. The Diagnostic Interview Schedule for Children-version IV, DISC-IV is a structured clinical interview of parents and is used to substantiate the clinical diagnosis. In addition, the DISC-IV also serves to diagnose the presence of comorbid disorders such as oppositional defiant disorder, conduct disorder, anxiety disorders and mood disorders. Children with a history of Tourette's syndrome, IQ lower than 70 on the Wechsler Intelligence Scale for Children-III[17], pervasive developmental disorder or psychosis were excluded from the study. Children with a previous history of intolerance or allergic reaction to MPH were also excluded from the study. When children had previously been on medication, a one week washout period was initiated prior to the start of the trial.

Study protocol

The core aspect of the study is a two week, double-blind, randomized, cross-over clinical trial with Methylphenidate (MPH) and placebo. The MPH and placebo pills are prepared by a pharmacist who is not involved in the study and the randomization is ensured by a research psychologist who did not have any patient contact. Following an initial week of baseline assessments, during which children are not taking any medication, children receive either placebo or 0.5 mg/kg of body weight of MPH divided into two equal doses (morning and noon) daily over a one week period and crossed over during the second week. While side-effects are monitored by the clinicians and by parents who fill out a side-effects rating scale (SE) during each week of treatment, no undue adverse events or grave SE were reported during the clinical trial.

During each week of the clinical trial, a battery of ecological, behavioral and laboratory measures were carried out and repeated during the following week. Teachers assessed the behavior at school by filling out the Conner's Global Index-Teacher's version (CON-T)[18], and parents assessed behavior at home by completing the Conner's Global Index-Parent's version (CON-P).[19] While teachers assessed the behavior during the school day, parents assessed behavior during the weekend after the child received the medication. Both CON-P and CON-T examine the frequency of ten types of ecologically relevant behavior and the results are organized into emotional-labile dimension (EL), restless-impulsive dimension (RS) and total score (TS).

On the morning of the third day of each week, children arrived to the clinic for a series of laboratory measures that were carried out by an experienced research assistant. This includes the Clinical Global Impression Scale (CGI-I)[20], the Restricted Academic Situation Scale (RASS),[21] and the Conner's Continuous Performance Task (CPT).[22] The CGI-I evaluates illness severity, RASS assesses specific behaviors (being off-task, fidgeting, playing with objects, vocalizing and being out of seat) during a 15 min of a classroom simulated setting, and the CPT measures impulse control along with sustained attention. The RASS and CPT are administered before and 60 minutes after the administration of each treatment. All the evaluations are completed by the same research assistant. The CPT Overall Index that provides an overall measure was used for

analysis rather than the individual sub-items that contributed to the Overall Index. This was done to reduce multiple testing errors and based on the fact that the overall measure would be more clinically meaningful rather than sub items for correlation analyses.

On the same day, children also undergo blood pressure (systolic blood pressure-SBP, diastolic blood pressure-DBP) and pulse measurements before and 60 minutes after administration of the pill. At the end of the trial and before breaking the code, the research team comprised of two experienced psychiatrists, a psychologist, child care workers and research assistants attributed a consensus clinical response (Group Impression Improvement or GPI) score taking into account all the available information from parents, teachers, ecological measures, and clinical assessments. A summary of the study schedule and measures is presented in Figure 1.

Statistical methods

The first analysis examined demographic parameters among children with ADHD and obtained summary means with standard deviations. This was followed by Pearson's Correlation analysis of interrelationship whenever baseline data was available prior to the start of the clinical trial. Similarly, side effects were examined using repeated measures analysis of variance ANOVA and the significant side-effects were used as covariates using a bivariate partial correlation analysis of TR interrelationship in the various observation settings (CON-P,CON-T, RASS, CPT, CGI-I and GPI). The significance of correlation coefficients (p), the direction of correlation and the magnitude of effect size (r) was examined for each correlation analysis.

Data were examined for assumptions to run the Pearson's correlation, and a non-parametric correlation was also used when deviations from normality were significant. These assumptions included running Q-Q (quantile-quantile) plots in SPSS to ensure that deviations from normality were minimal, ensuring linearity and visual examination for outliers. Bootstrap methods were used when there were minor deviations from normality and the results were confirmed with non-parametric analysis. The analysis was done using the statistical software package SPSS version 24.

Results

526 children (420-male, 106-female) with ADHD had an average age of 8.9 yrs (±1.8), an average IQ of 97 (±13.5), and an average total Child Behavioral Checklist (CBCL) score of 68.1 (± 8.3). A full summary of all the sample demographics is presented in table 1.

Table 2 presents the detailed summary of SE noted with MPH & placebo. The significant SE with MPH included insomnia, decreased appetite, stomachaches and headaches ($p<0.00$), and an increase in pulse (2 BPM) and Diastolic Blood Pressure (2 mm Hg). However, the placebo arm shows SE with a magnitude that is often similar to the MPH arm. The significant SE were then applied as covariates in the correlation analysis for TR.

Significant differences between MPH and placebo weeks (TR) were noted with all variables, the results are summarized in Table 3. The Pearson Correlation for CON-P and CON-T showed significant correlations at baseline and with CPT Overall Index baseline scores (the only laboratory measure available at baseline), the results are summarized in Table 4. With regard to TR, a bivariate correlation was done with the previously noted SE as covariates, the CON-P and CON-T showed a significant correlation only for RI and TS dimension ($p<0.03$). Table 5 presents a detailed summary of the correlations noted between parents and teachers at baseline and with TR.

No correlation was observed between TR as measured by the CON-P and CON-T on the one hand, and TR as measured by the CPT Overall Index, RASS and CGI-I changes scores on the other hand , the details are presented in table 6. However, TR as measured by CPT Overall Index, RASS, and CGI-I scores had significant bivariate correlations among themselves, the details are presented in table 7. Finally, the GPI which took into account all observations and was established after a consensual decision by the treating team upon reviewing all the results of the individual results of every subject and before unblinding the data, had significant correlations with all TR variables including the CON-P and CON-T, the details are presented in table 8. The effect size of the observed correlations ranged from relatively weak to medium effects, with the largest values seen for the correlations with GPI. Correspondingly, the actual proportion of

variance (r^2) accounted for by the observed effect sizes was small with the largest values seen for the correlations with GPI (e.g. r^2=0.04 for TR according to CON-T and CON-P, 0.09 for CPT Overall Index with RASS and, 0.32 for GPI with RASS). Correlation between GPI and the other variables is presented in Table 8. Finally, the significant side-effects with TR and the noted comorbidities at baseline did not have a statistically significant impact on the correlation between TR responses in various settings.

Discussion

In line with a large number of clinical trials[23,24], the present study shows that MPH has a consistent positive effect observed in all observation settings and according to several behavioral dimensions. This strongly suggests that there are elements of commonality that observers attribute to TR irrespective of the observation setting.

Previous studies have suggested that parent reports predict teacher-reported symptoms of inattention and hyperactivity.[25]. In line with these observations, the correlation analysis at baseline yielded significant correlations among parents (CON-P) and teachers (CON-T), further suggesting that irrespective of treatment, parents and teachers agree to a certain extent on some behavioral disturbances displayed by the child. Importantly, the significant correlation with CPT overall index baseline results suggests that parents and teacher's assessment share elements in common with the neuropsychological assessments at baseline. However, correlations among observers with regard to TR are less ubiquitous than the baseline correlations suggesting more heterogeneity in TR. Further, correlations between teacher evaluations (CON-T) and parent evaluations (CON-P) at baseline have a larger effect size as compared to with TR (r=0.26 at baseline, 0.10 with TR). In particular, the Connor's evaluations by parents and teachers with TR show significant correlations for RI dimension and total score dimension

There is a lack of correlation in TR between the parent/teacher scores on one hand and response as measured by the CPT Overall Index/RASS/CGI-I on the other hand. However, the CPT Overall index, RASS, CGI-I are correlated amongst themselves suggesting that the neuropsychological, classroom simulated and trained clinician assessments could tap into common elements of assessment. Finally, the observed result that GPI has significant

correlations with all observer settings and the largest noted effect size fully supports the clinical paradigm of integrating information from many available information sources.

Correlations of a small effect-size were noted among the observation settings, was best with GPI, followed by CPT Overall index/RASS/CGI-I, baseline observations and least for TR with parents and teachers. Previous studies have suggested that parent-teacher correlations are low for ADHD symptom assessment and appear to have different predictive value.[8,26,27] Further, parent-reports of ADHD symptoms appear to predict teacher-reported symptoms.[25,28,29] Correlations of a small effect size in our study support the hypothesis that there is important heterogeneity in assessing symptoms among various observers even at baseline prior to start of medications. This supports the notion that ADHD diagnosis requires information from many observers and raises significant questions regarding areas of psychopathology that each considers to be the most disabling.

The surprising result, that there is poor correlation with TR among the observers but that all observers note significant improvement in ADHD symptoms suggests several putative mechanisms, including: a) children might have intrinsically homogeneous improvement but observers notice specific elements of this improvement b) children might have heterogeneous improvement which vary with the observer c) children have heterogeneous improvement and observers have heterogeneous response criteria d) comorbidities and side effects result in observed results with MPH but play less of a role in placebo e) observed low correlation is partly due to parents and teachers assessments during different periods of the week which is intrinsic to the protocol. Studies also suggest that the instruments used by different observers might not be comparable and that there might be context-based and memory-based differences in assessment by parents and teachers.[8,30] Further, MPH given to ADHD children could have an effect on teacher's behavior.[31] Finally, the DSM requirement of clinically significant impairment in social, academic or occupational functioning could be interpreted differently by parents and teachers in the social and academic realms with distinct explanatory models by parents.[32]

While the significant side-effects were similar to previous reports during MPH and placebo weeks,[33,34] they (except for decreased appetite) did not modify the nature of TR seen by the

observers. Moreover, the presence of comorbidities did not have an impact on observer interrelationships. Both these findings are contrary to our initial expectations but are possibilities in the light of the observed small effect size of correlations and the observed poor correlation with TR. Moreover, both SE and comorbidities could have alternate mediating variables and account for some of the observed variance in TR among observers. The results do suggest that there are strong nocebo responses which limit the effect size of the SE which could be another reason for the largely insignificant role of SE as covariates. In support of this possibility, decreased appetite had the largest effect size among the observed significant side-effects and it had a statistically significant but small effect on the correlation of observer ratings between parents and teachers. Thus, in the presence of significant side-effects and comorbidity, clinical judgement does not appear to require more observation as observers have more inconsistency in TR.

In sum, the inconsistency noted with TR suggests that magnitude of improvement lies in the "eyes of the observer". This important result and the small effect sizes of the observed correlations suggest that measuring TR and titrating MPH needs information that is synthesized from several observers in a longitudinal fashion.[35] The wisdom of this approach is clearly illustrated by the large magnitude and universal correlation noted between GPI and all other observation settings.

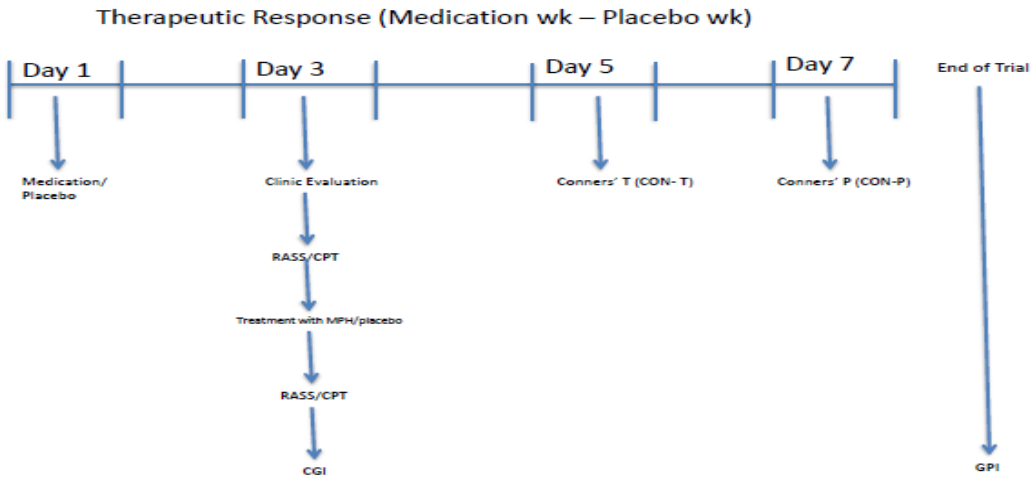
Strengths and Limitations

The study has one of the largest cohorts of children with ADHD in the world and is uniquely positioned to demonstrate differences among observation settings. However, large sample sizes can detect significant differences with small effect sizes which account for only a small proportion of the observed variance. The current study does not test hypothesis-based reasons for the observed heterogeneity and only provides possible leads for further investigation of TR and SE. Importantly, parents and teachers make assessments of therapeutic response during different periods of the week. The study had a preponderance of male children, which would be expected based on epidemiological estimates that ADHD among children is three times more common in boys rather than girls. In addition, the clinical and demographic characteristics are in line with known population prevalence estimates. This includes CBCL scores of more than 65 establishing

presence of ADHD, high presence of comorbidity with ODD being the most common form of comorbidity, Intelligence Quotient distribution in line with population averages for age, lower family income distribution in the presence of ADHD, and increased incidence of maternal smoking during pregnancy among children with ADHD. Thus, the sample study population is generalizable to the population of ADHD children who could be seen at other tertiary care referral clinics for children with ADHD.

Elements of the study such as unequal numbers by gender and lack of information regarding family member's ADHD status are practical difficulties in any study design for a project of a similar nature. Many of the children (more than two thirds) had previously been on medications prior to the two week washout period which could contribute to some of the study observations.

Figure 1 Measures Taken During the Treatment Week



1. CON-T (Conners' Teachers)
2. CON-P (Conners' Parents)
3. RASS (Restricted Academic Situation Scale)
4. CPT (Conners Continuous Performance Test)
5. CGI-I (Clinical Global Index)
6. GPI (Group Impression improvement)

Table 1: Demographic and Clinical Characteristics of the Sample of ADHD Children Included in the Study

	Overall
Age	8.9 (1.8)
Body Mass Index	18.5 (4.0)
Income[a]	9/57/72/70 59/293
CBCL Total Score	68.1 (8.3)
CBCL Internalizing	63.5 (9.9)
CBCL Externalizing	67.3 (9.9)
DISC Inattentive	7.0 (2.2)
DISC Hyperactive	5.4 (2.6)
DISC Impulsive	1.0 (1.0)
DISC Total	12.4 (3.8)
Any comorbidity (N/Y)	399/100
Conduct d/o[b]	485/34/50/12
ODD (N/Y)	339/243
Wisc FIQ	96.6 (13.5)
Wisc VIQ	94.9 (13.5)
Wisc PIQ	102.4 (14.2)
Birthweight	3362.2 (613.1)
Wks of gestation	38.8 (2.3)
Maternal smoking during pregnancy(N/Y)	358/195

All values are mean ± SD
a< $6,000, $6 - $10,000, $10 - $20,000,$20 - $30,000,$30 - $40,000,> $40,000
b- none/mild/moderate/severe
Child Behavir Checklist (CBCL), Diagnostic Interview Schedule (DISC), Oppositional Defiant Disorder (ODD), Wechsler Intelligence Scale for Children- Full scale Intelligence Quotient (FIQ), Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ)

Table 2: Side-Effects with Methylphenidate and Placebo Noted in the Study

	Placebo	Active	F/df/P Value
Insomnia	1.24 (2.3)	2.4 (3.1)	11.5/482/0.00
Nightmares	0.5 (1.5)	0.5 (1.5)	0.8/484/0.40
Stares a lot	1.0 (2.0)	1.0 (1.9)	3.3/483/0.07
Talks less	0.5 (1.6)	1.0 (2.0)	3.8/483/0.05
Uninterested	0.6 (1.7)	0.7 (1.7)	0.0/482/0.99
Decreased appetite	0.9 (2.0)	2.5 (3.0)	21.5/482/0.00
Irritable	2.4 (2.9)	2.4 (2.8)	1.6/480/0.20
Stomachaches	0.7 (1.8)	1.2 (2.2)	10.1/476/0.00
Headaches	0.7 (1.7)	1.3 (2.3)	11.3/479/0.00
Drowsiness	0.4 (1.3)	0.4 (1.3)	0.6/483/0.43
Sad	1.1 (2.1)	1.2 (2.3)	0.0/481/0.92
Prone to crying	1.2 (2.3)	1.5 (2.4)	0.2/482/0.62
Anxious	1.4 (2.2)	1.4 (2.3)	1.1/479/0.30
Bites fingernails	0.7 (2.0)	0.8 (2.1)	0.4/481/0.51
Euphoric	1.2 (2.3)	1.1 (2.1)	0.3/480/0.55
Dizziness	0.2 (0.7)	0.2 (1.0)	0.1/482/0.70
Tics	0.6 (1.7)	0.6 (1.8)	0.3/483/0.60
Pulse	77.7 (11.3)	79 (11.2)	4.2/1/0.04
SBP	104.0 (10.9)	104.7(10.9)	2.5/1/0.12
DBP	60.3 (10.2)	61.6 (11.1)	6.4/1/0.01

The placebo & active values are expressed as mean ± SD

Table 3: Significant Treatment Response (TR) with MPH noted in the Study

	MPH Week	Placebo Week	Significance
CON-P	56.6 (11.6)	62.5 (13.5)	9.9, 574, 0.00
CON-T	55.9 (11.4)	64.8 (13.1)	17.3, 577, 0.00
CPT	8.9 (9.9)	12.4 (10.4)	8.1, 531, 0.00
RASS	30.0 (23.5)	55.9 (29.8)	24.0, 620, 0.00
CGI-I	3.1 (1.0)	4.6 (0.9)	25.3, 578, 0.00
GPI	1.1 (0.4)	2.0 (0.4)	30.0, 580, 0.00

Conners Parents (CON-P), Conners Teachers (CON-T), Conners Continuous Performance Test Overall Index (CPT), Restricted Academic Situation Scale (RASS), Clinical Global Impression Scale (CGI-I), Group Impression Improvement (GPI)

Table 4: Correlation Between Conners Parent/ Teacher Observations at Baseline and CPT Overall index at Baseline Noted in the Study

	CPT Overall index Baseline
Conners Parents Global Index-Baseline	
Restless-Impulsive TR	R = 0.20, p = 0.00
Emotional-Labile TR	R= 0.12, p= 0.02
Total TR	R= 0.18, p=0.00
Conners Teachers Global Index-Baseline	
Restless-Impulsive TR	R=0.09, p= 0.05
Emotional-Labile TR	R=0.10, p=0.04
Total TR	R=0.10, p=0.04

TR = Conners' Global Index during placebo week minus Conners' Global Index during the methylphenidate week; Conners Continuous Performance Test Overall Index (CPT)

Table 5: Therapeutic Response Correlation Between Conners' Parents (CON-P) and Teachers Scores (CON-T) Noted in the Study

	Total (r, p-value)
Restless-Impulsive TR	0.15, 0.00
Emotional-Labile TR	0.08, 0.08
Total TR	0.10, 0.02
Restless-Impulsive Baseline	0.24, 0.00
Emotional-Labile Baseline	0.21, 0.00
Total Baseline	0.22, 0.00

TR = Therapeutic Response, Conners' Global Index during placebo week minus Conners' Global Index during the methylphenidate week

Table 6: Therapeutic Response Correlation Between Conners' Parents/Teachers' Evaluation, CPT Overall Index, RASS, CGI-I, and GPI noted in the Study

Conners Parents Global Index	CPT Overall index(r, p-value)	RASS(r, p-value)	CGI-I (r, p-value)	GPI(r, p-value)
Restless-Impulsive TR	0.06, 0.18	0.06, 0.14	0.07,0.09	0.31, 0.00
Emotional-Labile TR	0.10, 0.06	0.01, 0.75	0.05, 0.20	0.26, 0.00
Total TR	0.08, 0.07	0.05, 0.27	0.08, 0.10	0.30, 0.00
Conners Teachers Global Index				
Restless-Impulsive TR	0.01, 0.06	0.02, 0.59	0.08, 0.09	0.32, 0.00
Emotional-Labile TR	0.09, 0.07	0.02, 0.64	0.05, 0.28	0.22, 0.00
Total TR	0.09, 0.06	0.01, 0.74	0.07, 0.10	0.30, 0.00

TR = Therapeutic Response; Conners' Global Index during placebo week minus Conners' Global Index during the methylphenidate week

Conners Continuous Performance Test Overall Index (CPT), Restricted Academic Situation Scale (RASS), Clinical Global Impression Scale (CGI-I), Group Impression Improvement (GPI)

Table 7: Therapeutic Response Correlations Between CPT Overall Index, RASS and Clinical Observations (r, p-value) Noted in the Study

	CPT Overall index	RASS	CGI-I	GPI
CPT Overall index	N/A	0.31, 0.00	0.28, 0.00	0.30, 0.00
RASS	0.31, 0.00	N/A	0.55, 0.00	0.57, 0.00
CGI-I	0.28, 0.00	0.55, 0.00	N/A	0.64, 0.00
GPI	0.30, 0.00	0.57, 0.00	0.64, 0.00	N/A

Conners Continuous Performance Test Overall Index (CPT), Restricted Academic Situation Scale (RASS), Clinical Global Impression Scale (CGI-I), Group Impression Improvement (GPI)

Table 8: Correlation Between Group Impression Improvement and other scores (r, p-value)

Therapeutic response (TR) Scores	Group Impression Improvement Scores
CON-P Restless Impulsive	0.31, 0.00
CON-P Emotional Labile	0.26, 0.00
CON-P Total Scores	0.30, 0.00
CON-T Restless Impulsive	0.32, 0.00
CON-T Emotional Labile	0.22, 0.00
CON-T Total Scores	0.30, 0.00
CPT	0.30, 0.00
RASS	0.57, 0.00
CGI-I	0.64, 0.00

Conners Parents (CON-P), Conners Teachers (CON-T), Conners Continuous Performance Test Overall Index (CPT), Restricted Academic Situation Scale (RASS), Clinical Global Impression Scale (CGI-I), Group Impression Improvement (GPI)

Therapeutic Response in Children with ADHD: What is the Role of Child & Observers' Gender?

The following manuscript examines the role of gender of the observer (parent, teacher) and how it interacts with the gender of the child in evaluating TR as observed in several settings (home, school). Demographic and clinical characteristics of childhood ADHD are known to vary based on the child's gender. Further, educational literature in classroom settings suggests gender-based differences in evaluation. *However, to our knowledge, this work represents the first attempt to comprehensively examine the interaction between gender of the observer and gender of the child with ADHD in the context of TR* to MPH.

299 children (269-male, 30-female; average age 8.9±1.8) were evaluated by 52 male teachers, 212 female teachers; 269 female parents and 30 male parents. As expected, boys had more of the hyperactive phenotype ($p=0.00$), and significant TR was noted in all four observation settings ($P<0.00$). For baseline assessments, a significant interaction between teacher and child gender was noted. For the evaluation of TR, a significant interaction between teacher and child gender was noted for the RI dimension, and main effects were noted for the EL dimension and Total Score. Both for baseline assessments and TR, no interaction was noted between gender of the parent and gender of the child.

The observed interactions between the gender of children and teachers even after correction for hyperactivity suggest that a gender-based bias might contribute to the observed heterogeneity in evaluation of TR.

Manuscript 2

Therapeutic Response to Methylphenidate in ADHD: Role of Child and Observer Gender

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The article does not contain supporting information online.

Abstract

***Background*:** Gender-based differences have been described in children with Attention Deficit Hyperactivity Disorder (ADHD). The disorder is more prevalent in boys as compared to girls, and boys tend to have more of the hyperactive subtype. However, the interaction between the child's gender and the observer gender (parents & teachers) has not been examined in previous studies. This project aims to examine the interaction between the gender of the child and the gender of the observers (gender of teachers and gender of parents) on the therapeutic response (TR) and side effects (SE) noted with Methylphenidate in children with ADHD.

Methods: Children with ADHD undergo a two week double-blind, randomized, cross-over clinical trial with Methylphenidate (MPH) and placebo, and the information is obtained from various sources during each week. This includes the Conner's Global Index from parents (CON-P), teachers (CON-T), clinicians (CGI-I, GPI). The difference scores between the week of treatment with MPH and placebo was calculated for each measure to obtain the treatment response (TR) with MPH. Following examination of demographics for differences based on the gender of the parent and the teacher, the CON-T and CON-P were examined at baseline, and with TR for differences based on the gender of child and the observer by using a univariate ANCOVA correcting for any significant baseline covariates. Similarly, RASS, CPT Overall Index, CGI-I, and GPI were examined using a univariate ANCOVA correcting for any significant baseline covariates. Finally, the significant side-effects with TR were compared for gender-based differences of parent observer using a t-test.

Results: 299 children (269-male, 30-female; average age 8.9±1.8) were evaluated by 52 male teachers, 212 female teachers; 269 female parents and 30 male parents. Boys had more of the hyperactive phenotype ($p=0.00$). As expected, significant TR was noted in all observation settings ($P<0.00$). For the baseline week, the ANCOVA analysis for teachers yielded a significant teacher's gender x child's gender interaction. For the evaluation of TR, the ANCOVA analysis revealed a significant teacher's gender x child's gender interaction for the RI dimension, and main effects were noted for the EL and TS dimensions. Both for baseline and TR ANCOVA analyses, no parent' gender x child' gender interactions were noted.

Conclusion: The TR with MPH was consistently observed in all four observation settings suggesting that MPH improved outcomes. The observation that teachers had gender-based baseline interactions unlike parents suggests that there are differences in symptom assessment between parents and teachers at baseline based on the gender of the observer. Further, the observation that teachers note gender-based treatment differences with bigger improvement for male children while parents do not suggests that TR is observed differently based on requirements of observed settings. To our knowledge, this is the first paper to examine and demonstrate the nature of the interaction between gender of parent/teacher and the gender of child on symptoms of ADHD and response to MPH.

Introduction

Gender-based differences have been described in children with Attention Deficit Hyperactivity Disorder (ADHD).[36-41] The disorder is more prevalent in boys as compared to girls, and boys tend to have more of the hyperactive subtype.[37] In addition to cognitive and behavioral differences, differences in longitudinal course and outcome have been described based on the child's gender.[37,42,43] Further, more boys than girls appear to receive treatment for ADHD.[44] While the clinical and demographic features of ADHD have been well characterized as a function of the child's gender[41], there is no available literature looking into the interaction of the gender of the observer and the gender of the child in mediating treatment outcomes.

ADHD is the most commonly diagnosed psychiatric disorder in childhood and various biopsychosocial mechanisms have been implicated in the observed gender-based differences among children with ADHD.[45] Biological factors include hormonal, genetic, epigenetic, and other biological differences based in neural circuitry.[46,47] Psychological factors such as impulsivity, self-inhibition, and reward-related behavior have been implicated in ADHD. Environmental factors such as maternal smoking during pregnancy (MSDP) have been correlated with ADHD development, and differential effects of environmental adversity in ADHD have been described based on gender.[48] Sociological factors such as gender-role and school-related expectations have been thought to play a role in the observed differences in the prevalence of ADHD across the world.[49]

Similar to the biopsychosocial approach towards understanding the heterogeneity in the ADHD clinical phenotype, a biopsychosocial approach has been employed to appreciate the variability in TR and SE noted with stimulant medications such as MPH. Gender-based differences in pharmacokinetics attributed to the ADME (absorption, distribution, metabolism, excretion) mechanisms such as Liver enzyme and body fat distribution have been extensively reported.[50] Psychological factors such as increased aggression and oppositional behavior among boys could impact the TR and SE observed with MPH.[51] Further, the increased co-morbidity noted among male children with ADHD could contribute to a heterogeneous TR profile based on gender.

Finally, social factors such as gender-role based expectations could lead to differences in TR and SE profiles.[51]

Unlike adult psychiatric disorders, the assessment of ADHD is based on reports of the child's behavior as noted by observers such as parents and teachers which could contribute to greater variability in the ADHD-TR and SE phenotype.[4] Stimulants such as MPH have been demonstrated in clinical trials to reduce inattention and hyperactivity and enhance educational outcomes in children with ADHD.[52] The diagnosis and management of ADHD by the clinician is based on information obtained from parents and teachers, from clinical interviews, and when available from other measures such as the Conner's Performance Task (CPT) and the Restricted Academic Situation Scale (RASS). This information is used to begin stimulant treatments, and further titration to achieve optimal therapeutic response (TR) and minimal side effects (SE) is based on feedback from parents and teachers, and clinical observations of the child.[35] While biopsychosocial factors intrinsic to the child could contribute to the observed heterogeneity, factors unique to the observer could interact in dynamic ways with that of the child to account for some of the variability in TR and SE.[53]

In the context of examining gender-based differences in the ADHD, there are several studies looking into the clinical phenotype,[37] fewer studies that examine the TR and SE, and no studies that examine gender interaction in TR and SE. This project aims to delineate the interaction between the gender of teacher/parent with the child's gender in determining symptoms of ADHD and response to methylphenidate. Given the complex biopsychosocial aspects that come into play when a child with ADHD of a specific gender is evaluated by an observer of a specific gender, we hypothesized that gender-based interactions would vary based on the observational setting.

Methods

Subjects

The ADHD Pharmaco-behavioral study is an ongoing study at the Douglas Mental Health Research Institute in Montreal funded by the Canadian Institutes of Health Research. The current

study included a subset of all the subjects in this ongoing study as all the required measures were not available on all subjects. The protocol for the research study was approved by the Research Ethics Board of the Douglas Mental Health University Institute (DMHUI). Children are referred to the DMHUI by family doctors, teachers, community social workers, and pediatricians. These children were evaluated at the Disruptive Behavior Disorders Program and pediatric outpatient clinics of the DMHUI. Children diagnosed at these clinics with ADHD between the ages of 6 and 12 were recruited to the study. Following a detailed explanation of the study, parents provide written consent. Similarly, children gave their assent to participate in the study. More than ninety percent of the children invited to participate in the study by research assistants agreed to participate.

The clinical diagnosis of ADHD is made by experienced child psychiatrists. The diagnosis is based on DSM-IV criteria[16], dependent on clinical interviews of the child and requires the information provided to the clinician from at least one parent at the time of the clinical interview. The Diagnostic Interview Schedule for Children-version IV, DISC-IV is a structured clinical interview of parents and is used to substantiate the clinical diagnosis. In addition, the DISC-IV also serves to diagnose the presence of comorbid disorders such as oppositional defiant disorder, conduct disorder, anxiety disorders and mood disorders. Children with a history of Tourette's syndrome, IQ lower than 70 on the Wechsler Intelligence Scale for Children-III[17], pervasive developmental disorder or psychosis were excluded from the study. Children with a previous history of intolerance or allergic reaction to MPH were also excluded from the study. When children had previously been on medication, a one week washout period was initiated prior to the start of the trial.

Study protocol

The core aspect of the study is a two week, double-blind, randomized, cross-over clinical trial with Methylphenidate (MPH) and placebo. The MPH and placebo pills were prepared by a pharmacist who was not involved in the study and the randomization was ensured by a research psychologist who did not have any patient contact. Following an initial week of baseline assessments, during which children are not taking any medication, children received either placebo or 0.5 mg/kg of body weight of MPH divided into two equal doses (morning and noon)

daily over a one week period and crossed over during the second week. While side-effects are monitored by the clinicians and by parents who fill out a side-effects rating scale (SE) during each week of treatment, no undue adverse events or grave SE were reported during the clinical trial.

During each week of the clinical trial, a battery of ecological, behavioral and laboratory measures were carried out and repeated during the following week. Teachers assessed the behavior at school by filling out the Conner's Global Index-Teacher's version (CON-T)[18], and parents assessed behavior at home by completing the Conner's Global Index-Parent's version (CON-P).[19] While teachers assessed the behavior during the school day, parents assessed behavior during the weekend after the child received the medication. Both CON-P and CON-T examine the frequency of ten types of ecologically relevant behavior and the results are organized into emotional-labile (EL), restless-impulsive (RS) and total scores (TS) dimensions.

On the morning of the third day of each week, children arrived at the clinic for a series of laboratory measures that were carried out by an experienced research assistant. This includes the Clinical Global Impression Scale (CGI-I)[20], the Restricted Academic Situation Scale (RASS),[21] and the Conner's Continuous Performance Task (CPT).[22] The CGI-I evaluates illness severity, RASS assesses specific behaviors (being off-task, fidgeting, playing with objects, vocalizing and being out of seat) during a 15 min of a classroom simulated setting, and the CPT measures impulse control along with sustained attention. The RASS and CPT are administered before and 60 minutes after the administration of each treatment. All the evaluations are completed by the same research assistant.

On the same day, children also undergo blood pressure (systolic blood pressure-SBP, diastolic blood pressure-DBP) and pulse measurements before and 60 minutes after administration of the pill. At the end of the trial and before breaking the code, the research team comprised of two experienced child psychiatrists, a psychologist, child care workers and research assistants attributed a consensus clinical response (Group Impression Improvement or GPI) score taking into account all the available information from parents, teachers, ecological measures, and clinical assessments. A summary of the study schedule and measures is presented in Figure 1.

Statistical methods

The initial analysis examined demographic parameters among children with ADHD, followed by the examination of gender-based differences in these demographic parameters using Analysis of Variance (ANOVA) or Chi-squared methods depending on whether the data was continuous or categorical in nature. The demographic data were then examined for any differences based on the gender of the parent and the teacher using an ANOVA. Any significant demographic variables were then used as covariates in subsequent ANCOVA analyses. The difference between the MPH and placebo weeks was used to obtain the therapeutic response (TR). The CON-T, CON-P, and CPT Overall Index were then separately examined for baseline and TR scores for differences based on the gender of the child and the observer by using a univariate ANCOVA.

The multi factor ANCOVA used the CONNERS' score (parents or teacher) as the continuous outcome variable and gender of the child (male vs. female) and gender of the observer (male vs females) are the two independent factors. Similarly, RASS, CPT Overall Index, and clinician-based scores were examined for differences based on child's gender using an ANCOVA analysis. Finally, side-effects were examined with a t-test, and the significant side-effects were observed for gender-based differences of child and parent observer using ANOVA. Prior to every analysis, the data were examined for assumptions of parametric methods. This included visual examination of the data for outliers, homogeneity of variance, independence of predictor and covariate, and ensuring that the deviations from normality was minimal. Bootstrap methods were employed when minor deviations from normality were noted. The analysis was done using the statistical software package SPSS version 24.

Results

299 children (269-male, 30-female) with ADHD had an average age of 8.9 (±1.8) and BMI of 18.5 (± 4.0), an average IQ of 97 (±13.5), and had a total Child Behavioral Checklist (CBCL) score of 68.1 (± 8.3). Boys had more of the hyperactive subtype (p=0.00), no differences were noted among the other demographic parameters, a summary of the information is presented in table 1.

The CON-T included information from 52 male teachers, 212 female teachers, and the CON-P had information from 269 female parents and 30 male parents. Table 2 presents demographics of ADHD children by teacher's gender and limited gender-based demographic differences were noted. This includes the age of the child being slightly older, lower incomes, increased prevalence of conduct disorder and lower weeks of gestation under male teachers. Table 3 presents demographics of ADHD children by parent's gender and no gender-based demographic differences apart from age were noted. A significant effect was noted for TR for CON-T, CON-P and other measures as presented in table 4.

Figure 2 presents teacher Conner's Global Index scores (emotional-labile-EL, restless-impulsive-RI, and total scores-TOT) with TR by gender. The univariate ANCOVA included hyperactivity, birth weight, age, weeks of gestation, income and conduct disorder as covariates. The univariate ANCOVA analysis for teachers suggested significant gender-based interactions for both dimensions at baseline and only with RI dimension for TR ($p<0.00$). The EL dimension and TS showed main effects but no gender interactions with TR ($p<0.05$). Post-hoc analysis at baseline suggested that for the RI dimension, female teachers, compared to male teachers, found girls to be more severe; for the EL dimension, male teachers found boys to be more severe and the overall TS dimension score was a combination of male teachers finding boys more severe and female teachers noting that girls were more severe. Post-hoc analysis with TR suggested that for the RI dimension, male teachers found boys showed more improvement; for the EL and TS dimensions, boys were found to have more overall improvement than girls. Notably, the significant results were driven by effect sizes of a small magnitude. Figure 2 demonstrates the interaction noted between gender of teacher and gender of the child at baseline and with TR respectively. The analysis corrected (taken as covariates) any significant demographic differences between boys and girls, including any age related differences. When the boys and girls were separated into 2 categories based on age (middle split, younger vs older), no significant differences were seen in therapeutic response.

Figure 3 presents parent Conner's Global Index scores at baseline and with TR by gender. For parents, no interaction was noted between gender of parent and child both at baseline and for TR

with the univariate ANCOVA. Further, with TR no main effects were noted, while at baseline, significant main effects were noted ($p<0.05$). Parents noted higher scores for female children for the RI and TS dimensions at baseline.

Table 5 presents CPT, RASS scores by gender. While overall significant improvement was seen with TR on all scores, no differences were noted with TR based on gender for these scores. Further, there were no differences noted at baseline for any of the scores. Table 6 presents the significant overall SE with MPH which included insomnia, decreased appetite, stomachaches and headaches ($p<0.00$), and an increase in pulse (2 BPM) and Diastolic Blood Pressure (2 mm Hg).

Discussion

While there is extensive literature on gender differences in ADHD, to our knowledge, the present study is the first attempt to comprehensively examine and demonstrate the interaction between the gender of parent/teacher and the gender of child in TR in ADHD.

The demographic differences based on teachers' gender suggest that among children with ADHD, male teachers appeared to be assigned to slightly older boys with lower family incomes, and more severe conduct disorder. In addition, the weeks of gestational age at birth is less under male teachers which could partly be due to the noted lower family incomes and higher comorbidity. While these findings could be a feature specific to this study, it would be interesting to query if schools tend to make student assignments that take particular demographics of the child into account.

The TR with MPH was consistently observed in all observation settings suggesting that MPH improved outcomes. This includes consistent and statistically significant TR in every observation setting suggesting that a true response was noted irrespective of the observer. It firmly supports the hypothesis that there are shared elements of commonality that observers attribute to TR irrespective of the observation setting.

For the baseline analysis, there are differences in symptom assessment between parents and teachers with interactions between the gender of the observer and the gender of the child noted only for teachers suggesting that some aspects of the symptoms might be assessed differently [54]. For all dimensions (TS, RI, EL), female teachers found girls to be more severe, and male teachers found boys to be more severe. Teachers could have limited contact with children as compared to parents who have known the child since birth. Further, parents could have alternate explanatory models for ADHD based on gender.[32] Gender-based differences have been reported in the achievement goals of children with ADHD.[55]Many of the children (more than two thirds) had previously been on medications prior to the two week washout period which could contribute to some of the study observations, especially by teachers. In addition, in the presence of large class sizes, teachers might have limited contact with children.[8]

For the TR analysis, there are differences in symptom assessment between parents and teachers with interactions noted only for teachers when children have more severe RI dimension scores, and male teachers observe that boys show more improvement than girls. Gender-based differences have been described in educational assessments in classroom settings,[56] which could be amplified in ADHD and in TR and SE to treatments for ADHD.[31] In the presence of comorbidities such as Intellectual Handicap and Oppositional Defiant Disorder which are more commonly seen among male children, gender-differences can influence teacher assessments .[15] Importantly, various internalized gender-roles and expectations could lead to variations ascribed to TR.

Interestingly, teachers overall (irrespective of teacher gender) find that boys demonstrate more TR than girls. Cross-cultural differences have also been noted in teacher perceptions of classroom interventions (behavioral vs pharmacological) in ADHD in the United States and New Zealand, and interactions have been demonstrated between student gender, nationality, and intervention preference.[57] Moreover, teacher expectations have been shown to vary, and teachers have been shown to rate children with ADHD, and children with ADHD stimulant treatment labels less favourably than children with no labels.[58] The results support previous literature examining psychometric properties of the parent and teacher ADHD rating scale suggesting that

parents and teachers have different frames of reference when rating ADHD symptoms, with evidence for differential item functioning across gender and age for specific items within subscales.[59]

While the observed SE by parents are similar to that expected from other studies[33,34] and there are strong nocebo responses that reduce the effect size, all the SE except for decreased appetite do not show any gender-based differences. With MPH, gender and weight status have been found in previous studies to have moderating effects on suppression of appetite and food consumption in healthy adults.[60]

In comparison to results across observation settings, the observation that teachers note a gender-based TR interaction while parents do not suggests that TR is observed differently based on requirements of observed settings. While teachers assess TR during the week, parents assess TR at the end of the week and this could have an impact as teachers might note the immediate effects of the medications. Disruptive behaviours have been shown to have an impact on the agreement between parents and teachers.[61] However, the finding that teachers observe interactions with TR while parents observe only main effects at baseline suggests that there are differences between parent and teacher evaluations that contribute to heterogeneity in treatment response, suggesting that parents and teachers might have gender-based expectations of child behavior & TR.

In sum, the observed interaction among genders of the observer and the observed that differs at baseline and with TR suggests that the there might be a complex interplay of bias, particularly for *the RI dimension*. An alternate possibility is that the observer indeed induces a change in the behavior of the observed as a function of each other's gender. However, the fact that only teachers note the interaction and not parents, as a function of their gender makes this a less likely possibility.

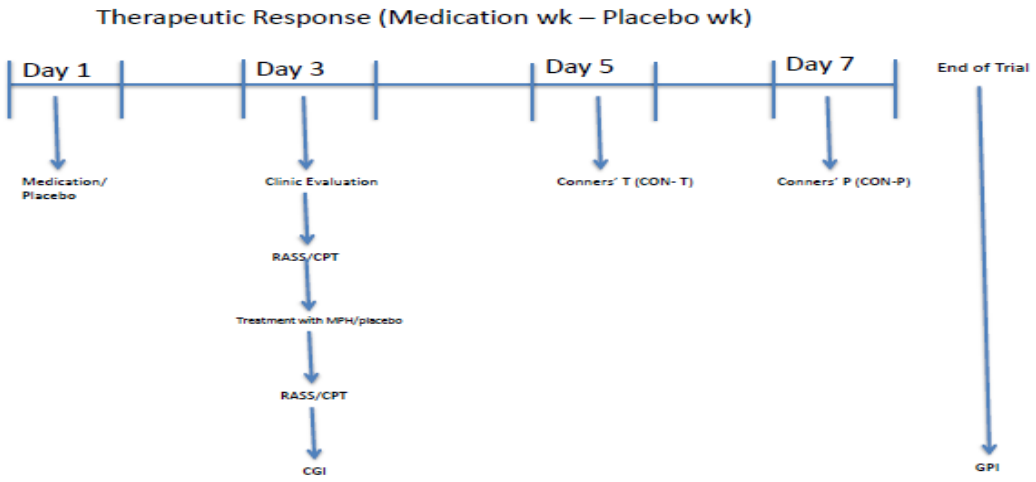
Strengths and limitations

The study had a preponderance of male children which would be expected based on epidemiological estimates that ADHD among children is three times more common in boys

rather than girls. In addition, the clinical and demographic characteristics are in line with known population prevalence estimates.

The study had information from more female teachers and parents but had a sizeable number of reports from male teachers and parents. While this study represents the largest study of its nature to date, it would have been ideal to have equal gender distribution among parents, teachers, and children for questions relating to statistical comparisons. However, with 52 male teachers, 212 female teachers, and 269 female parents and 30 male parents, and 269-male and 30-female children, the sample sizes are reasonably powered to draw conclusions. Moreover, the gender distributions of parents, teachers, and subjects with ADHD follows expected population estimates in gender distribution. Elements of the study such as unequal numbers by gender and lack of information regarding family member's ADHD status are practical difficulties in any study design for a project of a similar nature. This study is the first to demonstrate interactions between gender of teacher and child, it would also be important for future studies to examine the reasons for the observed heterogeneity in TR & SE, including gender role and expectations of parents and teachers.

Figure 1: Measures Taken During the Treatment Week

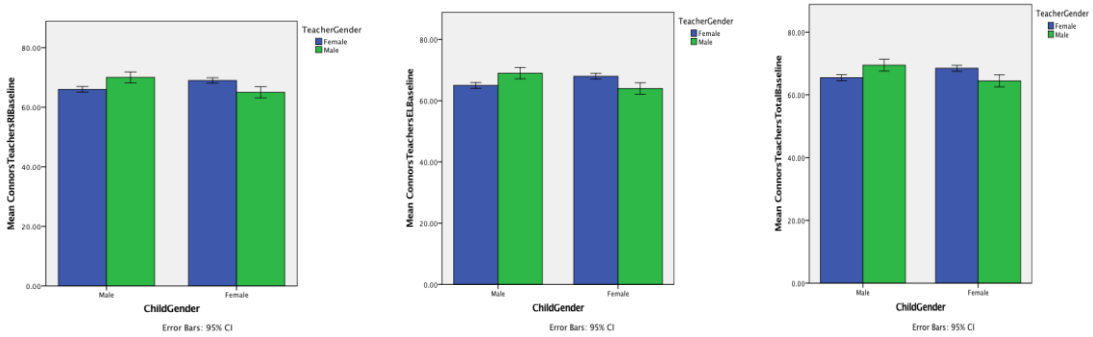


1. CON-T (Conners' Teachers)
2. CON-P (Conners' Parents)
3. RASS (Restricted Academic Situation Scale)
4. CPT (Conners Continuous Performance Test)
5. CGI-I (Clinical Global Index)
6. GPI (Group Impression improvement)

Figure 2: Conners Teacher Scores at Baseline and with Therapeutic Response Separated by Teacher's and Child's Gender

A. Significant Differences at Baseline

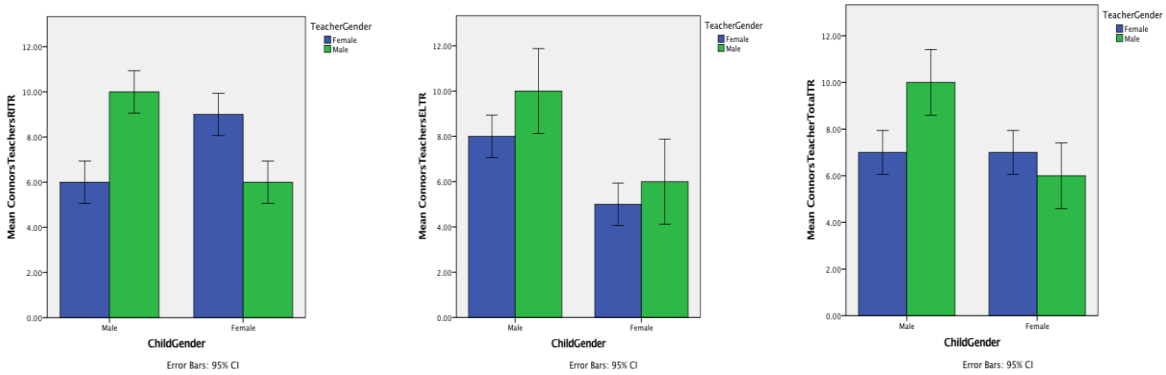
1 2 3



1. Child's Gender x Teacher's gender (F/P=6.6/0.01)
2. Child's Gender x Teacher's gender (F/P=8.8/0.00)
3. Child's Gender x Teacher's gender (F/P=10.9/0.00)

B. Significant Differences With Therapeutic Response

1 2 3

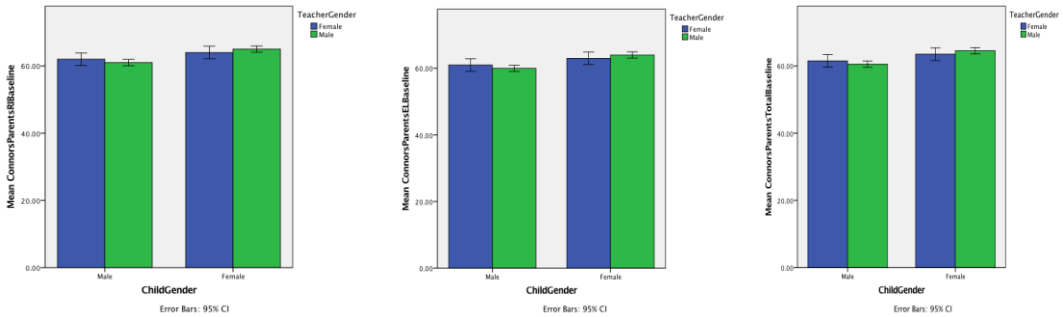


1. Child's Gender x Teacher's gender (F/P= 3.8/0.05)
2. Child's Gender (F/P= 4.3/0.04)
3. Child's Gender (F/P=4.2/0.04); Teacher's Gender (F/P=6.1/0.01)

Figure 3: Conners Parent Scores at Baseline and with Therapeutic Response Separated by Parent's and Child's Gender

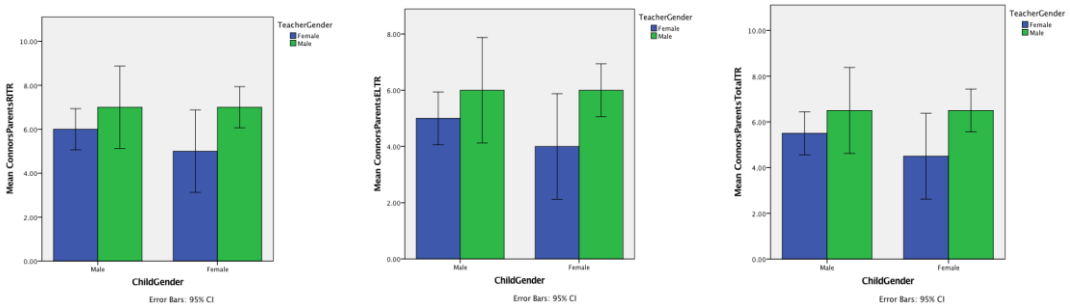
A. Significant Differences at Baseline

1 2 3



1. Child's Gender (F/P= 22.2/0.00)
2. Child's Gender (F/P= 17.0/0.00)

B. No Significant Differences With Therapeutic Response



Tables

Table 1: Demographic and Clinical Characteristics of the Sample of ADHD Children Included in the Study

	Overall (299)	Male (269)	Female (30)	F/X^2/df/ P
Age	8.9 (1.8)	8.9 (1.8)	9.1 (1.8)	0.3/1/0.58
BMI	18.5 (4.0)	18.4 (4.0)	18.6 (4.2)	0.2/1/0.66
Income[a]	9/57/72/70 59/293	9/50/59/51 51/222	0/7/13/19/8 71	10.7/5/0.06
CBCL Total Score	68.1 (8.3)	68.4 (8.1)	67.3 (9.2)	1.7/1/0.19
CBCLInternalizing	63.5 (9.9)	63.7 (9.5)	62.6 (11.5)	1.2/1/0.28
CBCLExternalizing	67.3 (9.9)	67.6 (9.7)	66.1 (10.5)	2.0/1/0.15
DISC Inattentive	7.0 (2.2)	6.9 (2.2)	7.2 (2.1)	2.1/1/0.15
DISCHyperactive	5.4 (2.6)	5.6 (2.6)	4.8 (2.7)	*9.3/1/0.00*
DISC Impulsive	1.0 (1.0)	2.1 (1)	1.9 (1.1)	3.3/1/0.07
DISC Total	12.4 (3.8)	12.5 (3.8)	12.0 (3.7)	1.6/1/0.20
Any comorbidity (N/Y)	399/100	325/72	74/28	6.4/3/0.09
Conduct d/o[b]	485/34/50/12	374/29/44/11	111/5/6/1	5.4/3/0.14
ODD (N/Y)	339/243	273/186	66/57	1.3/1/0.24
Wisc FIQ	96.6 (13.5)	96.8 (13.9)	95.8 (11.9)	0.4/1/0.51
Wisc Verbal IQ	94.9 (13.5)	94.5 (13.7)	96.7 (12.4)	2.3/1/0.12
Wisc Perf IQ	102.4 (14.2)	102.9 (14.2)	100.5 (14.1)	2.6/1/0.11
Birthweight	3362.2 (613.1)	3392.8 (622.3)	3236.1 (558.7)	5.5/1/0.02
Wks of gestation	38.8 (2.3)	38.8 (2.3)	39.1 (2.1)	1.4/1/0.23
Maternal smoking during pregnancy(N/Y)	358/195	287/155	71/40	0.0/1/0.85

a< $6,000, $6 - $10,000, $10 - $20,000,$20 - $30,000,$30 - $40,000,> $40,000
b- none/mild/moderate/severe

Child Behavir Checklist (CBCL), Diagnostic Interview Schedule (DISC), Oppositional Defiant Disorder (ODD), Wechsler Intelligence Scale for Children- Full scale Intelligence Quotient (FIQ), Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ)

Table 2: Demographic and Clinical Characteristics ADHD children By Teacher's Gender

	Overall (264)	Male Teacher (52)	Female Teacher (212)	F or X^2/df/ P
Age	9.0 (1.8)	9.5 (2.0)	8.9 (1.8)	*9.8/1/0.01*
BMI	18.5 (4.0)	19.4 (4.7)	18.3 (4.0)	3.6/1/0.06
Income[a]	9/57/72/70 59/293	0/14/12/16 12/31/85	9/57/72/70 59/293	14.8/5/0.01
CBCL Total Score	68.1 (8.3)	69.1 (7.9)	68.0 (8.4)	1.3/1/0.25
CBCLInternalizing	63.5 (9.9)	63.9 (9.6)	63.4 (10.0)	0.2/1/0.62
CBCLExternalizing	67.3 (9.9)	69.0 (10.7)	67.0 (9.7)	3.0/1/0.08
DISC Inattentive	7.0 (2.2)	6.8 (2.7)	7.0 (2.1)	0.6/1/0.44
DISCHyperactive	5.4 (2.6)	5.4 (2.7)	5.4 (2.6)	0.0/1/0.87
DISC Impulsive	2.1 (1.0)	2.1 (1.0)	2.1 (1.0)	0.4/1/0.51
DISC Total	12.4 (3.8)	12.2 (4.0)	12.4 (3.8)	0.3/1/0.56
Any comorbidity (N/Y)	100/399	15/56	85/343	1.9/3/0.58
Conduct d/o[b]	485/34/50/12	61/8/11/6	424/26/39/6	*17.8/3/0.00*
ODD (N/Y)	339/243	58/28	281/215	3.5/1/0.06
Wisc FIQ	96.6 (13.6)	96.6 (12.6)	96.6 (13.6)	0.0/1/0.98
Wisc Verbal IQ	94.9 (13.5)	94.0 (11.8)	95.1 (13.8)	0.5/1/0.47
Wisc Perf IQ	102.4 (14.2)	102.4 (12.9)	102.4 (14.4)	0.0/1/0.90
Birthweight	3362.2 (613.1)	3398 (606.4)	3355.9 (614.8)	0.3/1/0.57
Wks of gestation	38.8 (2.3)	38.2 (3.1)	39.0 (2.1)	*0.6/1/0.02*
Maternal smoking during pregnancy(N/Y)	358/195	47/36	311/159	2.8/1/0.09

a< $6,000, $6 - $10,000, $10 - $20,000,$20 - $30,000,$30 - $40,000,> $40,000
b- none/mild/moderate/severe
Child Behavir Checklist (CBCL), Diagnostic Interview Schedule (DISC), Oppositional Defiant Disorder (ODD), Wechsler Intelligence Scale for Children- Full scale Intelligence Quotient (FIQ), Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ)

Table 3: Demographic and Clinical Characteristics of ADHD Children By Parents' Gender

	Overall (299)	Mother (269)	Father (30)	F/X^2/df/ P
Age	9.0 (1.8)	8.9 (1.8)	9.5 (1.8)	9.2/1/0.00
BMI	18.5 (4.0)	18.4 (4.0)	18.6 (4.2)	0.0/1/0.99
Income[a]	9/57/72/70 59/293	8/52/60/65 53/249	1/5/12/5 6/44	5.4/5/0.37
CBCL Total Score	68.1 (8.3)	68.4 (8.1)	67.3 (9.2)	0.9/1/0.33
CBCLInternalizing	63.5 (9.9)	63.7 (9.5)	62.6 (11.5)	2.5/1/0.11
CBCLExternalizing	67.3 (9.9)	67.6 (9.7)	66.1 (10.5)	0.3/1/0.61
DISC Inattentive	7.0 (2.2)	6.9 (2.3)	7.2 (2.1)	0.6/1/0.44
DISCHyperactive	5.4 (2.6)	5.6 (2.6)	4.8 (2.7)	3.1/1/0.08
DISC Impulsive	2.0 (1.1)	2.1 (0.1)	1.9 (1.1)	2.7/1/0.10
DISC Total	12.4 (3.8)	12.5 (3.8)	12.0 (3.7)	2.8/1/0.09
Any comorbidity (N/Y)	100/399	85/352	15/47	2.2/3/0.53
Conduct d/o[b]	485/34/50/12	423/30/41/12	62/4/9/0	3.0/3/0.39
ODD (N/Y)	339/243	290/217	49/26	1.8/1/0.18
Wisc FIQ	96.6 (13.5)	96.8 (13.9)	95.9 (11.9)	1.2/1/0.27
Wisc Verbal IQ	95.0 (13.5)	94.5 (13.7)	97.0 (12.4)	0.3/1/0.58
Wisc Perf IQ	102.4 (14.2)	102.9 (14.2)	100.5 (14.1)	0.1/1/0.73
Birthweight	3362.2 (613.1)	3392.8 (622.3)	3236.1 (558.7)	0.1/1/0.79
Wks of gestation	38.8 (2.3)	38.8 (2.3)	39.1 (2.1)	0.5/1/0.46
Maternal smoking during pregnancy(N/Y)	358/195	317/174	41/21	0.1/1/0.80

a< $6,000, $6 - $10,000, $10 - $20,000,$20 - $30,000,$30 - $40,000,> $40,000
b- none/mild/moderate/severe

Child Behavir Checklist (CBCL), Diagnostic Interview Schedule (DISC), Oppositional Defiant Disorder (ODD), Wechsler Intelligence Scale for Children- Full scale Intelligence Quotient (FIQ), Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ)

Table 4: Significant Treatment Response (TR) with MPH Noted in the Study

	MPH Week	Placebo Week	Significance
CON-P	56.6 (11.6)	62.5 (13.5)	9.9, 574, 0.00
CON-T	55.9 (11.4)	64.8 (13.1)	17.3, 577, 0.00
CPT	8.9 (9.9)	12.4 (10.4)	8.1, 531, 0.00
RASS	30.0 (23.5)	55.9 (29.8)	24.0, 620, 0.00
CGI-I	3.1 (1.0)	4.6 (0.9)	25.3, 578, 0.00
GIP	1.1 (0.4)	2.0 (0.4)	30.0, 580, 0.00

Conners Parents (CON-P), Conners Teachers (CON-T), Conners Continuous Performance Test Overall Index (CPT), Restricted Academic Situation Scale (RASS), Clinical Global Impression Scale (CGI-I), Group Impression Improvement (GPI)

Table 5: Classroom Simulation Scores (CPT Overall Index & RASS) By Gender

	Total (279)	Male ADHD (220)	Female ADHD (59)
CPT Baseline week	6.3 (0.6)	6.4 (0.1)	6.0 (1.2)
CPT-TR	-3.5 (0.6)	-3.3 (0.7)	-4.1 (1.3)
RASS-TR	-27.5 (1.6)	29.0 (1.8)	22.2 (3.6)
CGI-I-Clinical Staff TR	-1.5 (0.1)	-1.5 (0.1)	-1.5 (0.1)
Group Imp TR	1.8 (0.1)	1.9 (0.1)	1.6 (0.1)

TR = Conners' Global Index during placebo week minus Conners' Global Index during the methylphenidate week; Conners Continuous Performance Test Overall Index (CPT)

Table 6: Side-Effects with Methylphenidate and Placebo Noted in the Study

	Placebo	Active	F/df/P Value
Insomnia	1.24 (2.3)	2.4 (3.1)	11.5/482/0.00
Nightmares	0.5 (1.5)	0.5 (1.5)	0.8/484/0.40
Stares a lot	1.0 (2.0)	1.0 (1.9)	3.3/483/0.07
Talks less	0.5 (1.6)	1.0 (2.0)	3.8/483/0.05
Uninterested	0.6 (1.7)	0.7 (1.7)	0.0/482/0.99
Decreased appetite[1]	0.9 (2.0)	2.5 (3.0)	21.5/482/0.00
Irritable	2.4 (2.9)	2.4 (2.8)	1.6/480/0.20
Stomachaches	0.7 (1.8)	1.2 (2.2)	10.1/476/0.00
Headaches	0.7 (1.7)	1.3 (2.3)	11.3/479/0.00
Drowsiness	0.4 (1.3)	0.4 (1.3)	0.6/483/0.43
Sad	1.1 (2.1)	1.2 (2.3)	0.0/481/0.92
Prone to crying	1.2 (2.3)	1.5 (2.4)	0.2/482/0.62
Anxious	1.4 (2.2)	1.4 (2.3)	1.1/479/0.30
Bites fingernails	0.7 (2.0)	0.8 (2.1)	0.4/481/0.51
Euphoric	1.2 (2.3)	1.1 (2.1)	0.3/480/0.55
Dizziness	0.2 (0.7)	0.2 (1.0)	0.1/482/0.70
Tics	0.6 (1.7)	0.6 (1.8)	0.3/483/0.60
Pulse	77.7 (11.3)	79 (11.2)	4.2/1/0.04
SBP	104.0 (10.9)	104.7(10.9)	2.5/1/0.12
DBP	60.3 (10.2)	61.6 (11.1)	6.4/1/0.01

1. Significantly different based on parents and teacher's gender; The placebo & active values are expressed as mean ± SD

Final Conclusions and Summary

The two studies support the hypothesis that there is heterogeneity in TR based on the observer settings and gender, particularly during the treatment weeks. However, all observers note overall improvement with MPH suggesting that there are commonalities among all observers. The results give new perspectives on approaching information gathered from several sources, and strongly support current treatment titration approaches that attempt a synthesis of vantage points, taking into account variables such as observer settings and gender.

While the results need to be replicated followed by hypothesis-driven examination of reasons behind the apparent heterogeneity, the results point towards several putative mechanisms. First, the small effect size of inter-rater correlations during baseline week and lack of correlation during treatment week could be due to heterogeneity in improvement of individual symptoms of ADHD with MPH. In addition, intrinsic aspects of the protocol could have contributed to some of the observed heterogeneity. Second, parents and teachers might observe children during different time points after MPH administration which could contribute to the noted differences, and parents might observe differences based on their own ADHD status. Third, parents and teachers could have different performance tasks that they value and have implicit gender-based assumptions and expectations. In addition, children could in turn have ingrained these implicit assumptions introducing a gender-bias. Fifth, while the role of side-effects in modulating the observed TR among observers appears minimal, the strong placebo (and nocebo) responses noted on SE could contribute to minimizing the overall impact of SE on observed TR. Finally, the results are based on a rigorously conducted two week RCT, longer-term results and longitudinal follow-up assessments of TR and SE could substantiate the observed findings and shed further light on putative mechanisms behind the observed heterogeneity.

In sum, the responses to the two key questions raised in the introduction relating to *TR observed with MPH are as follows*:

1. There is significant heterogeneity among observers with some areas of commonality.

2. There is an interaction between the gender of the teacher and child specifically for the RI dimension, and there is no interaction between the gender of the parent and the child.

References

1 Thomas, R., Sanders, S., Doust, J., Beller, E. & Glasziou, P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* **135**, e994-e1001 (2015).

2 Barkley, R. A. *Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment*. (Guilford Publications, 2014).

3 ATTENTION-DEFICIT, S. O. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, peds. 2011-2654 (2011).

4 Brock, S. E. & Clinton, A. Diagnosis of attention-deficit/hyperactivity disorder (AD/HD) in childhood: A review of the literature. *The California School Psychologist* **12**, 73-91 (2007).

5 McGee, R. A., Clark, S. & Symons, D. Does the conners' continuous performance test aid in ADHD diagnosis? *Journal of abnormal child psychology* **28**, 415-424 (2000).

6 Conners, C. K. Clinical use of rating scales in diagnosis and treatment of attention-deficit/hyperactivity disorder. *Pediatric Clinics of North America* **46**, 857-870 (1999).

7 Tripp, G., SCHAUGHENCY, E. A. & Clarke, B. Parent and teacher rating scales in the evaluation of attention-deficit hyperactivity disorder: contribution to diagnosis and differential diagnosis in clinically referred children. *Journal of Developmental & Behavioral Pediatrics* **27**, 209-218 (2006).

8 De Los Reyes, A. & Kazdin, A. E. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. *Psychological bulletin* **131**, 483 (2005).

9 Sessa, F. M., Avenevoli, S., Steinberg, L. & Morris, A. S. Correspondence among informants on parenting: Preschool children, mothers, and observers. *Journal of Family Psychology* **15**, 53 (2001).

10 Mitsis, E. M., McKAY, K. E., Schulz, K. P., Newcorn, J. H. & Halperin, J. M. Parent–teacher concordance for DSM-IV attention-deficit/hyperactivity disorder in a clinic-referred sample. *Journal of the American Academy of Child & Adolescent Psychiatry* **39**, 308-313 (2000).

11 Valo, S. & Tannock, R. Diagnostic instability of DSM–IV ADHD subtypes: Effects of informant source, instrumentation, and methods for combining symptom reports. *Journal of clinical child & adolescent psychology* **39**, 749-760 (2010).

12 Rohde, L. A. *et al.* Exploring different information sources for DSM-1V ADHD diagnoses in Brazilian adolescents. *Journal of Attention Disorders* **3**, 91-96 (1999).

13 Wåhlstedt, C., Thorell, L. B. & Bohlin, G. Heterogeneity in ADHD: neuropsychological pathways, comorbidity and symptom domains. *Journal of abnormal child psychology* **37**, 551-564 (2009).

14 Faraone, S. V., Biederman, J. & Zimmerman, B. Correspondence of parent and teacher reports in medication trials. *European child & adolescent psychiatry* **14**, 20-27 (2005).

15 Achenbach, T. M., McConaughy, S. H. & Howell, C. T. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychological bulletin* **101**, 213 (1987).
16 Association, A. P. Diagnostic and statistical manual of mental disorders DSM-IV-TR fourth edition (text revision). (2000).
17 Wechsler, D. *WISC-III: Wechsler intelligence scale for children: Manual*. (Psychological Corporation, 1991).
18 Conners, C. K., Sitarenios, G., Parker, J. D. & Epstein, J. N. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of abnormal child psychology* **26**, 257-268 (1998).
19 Conners, C. K., Sitarenios, G., Parker, J. D. & Epstein, J. N. Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. *Journal of abnormal child psychology* **26**, 279-291 (1998).
20 Guy, W. National Institute of Mental Health. CGI–Clinical Global Impression. *Manual for the ECDEU Assessment Battery* **2**, 12-11.
21 Milich, R., Loney, J. & Landau, S. Independent dimensions of hyperactivity and aggression: A validation with playroom observation data. *Journal of Abnormal Psychology* **91**, 183 (1982).
22 Conner, C. Conner's continuous performance test. *North Tonawanda (NY): Multi-Health Systems* (1995).
23 Faraone, S. V. & Buitelaar, J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *European child & adolescent psychiatry* **19**, 353-364 (2010).
24 Wolraich, M. L. *et al.* Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* **108**, 883-892 (2001).
25 Zeiner, P. Parent-reported symptoms of hyperactivity and attention deficits predict teacher-reported symptoms. *Acta Paediatrica* **86**, 178-182 (1997).
26 Murray, D. W. *et al.* Parent versus teacher ratings of attention-deficit/hyperactivity disorder symptoms in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS). *Journal of Child and Adolescent Psychopharmacology* **17**, 605-619 (2007).
27 Verhulst, F. C., Koot, H. M. & Van der Ende, J. Differential predictive value of parents' and teachers' reports of children's problem behaviors: A longitudinal study. *Journal of abnormal child psychology* **22**, 531-546 (1994).
28 Biederman, J., Faraone, S. V., Milberger, S. & Doyle, A. Diagnoses of attention-deficit hyperactivity disorder from parent R predict diagnoses based on teacher reports. *Journal of the American Academy of Child & Adolescent Psychiatry* **32**, 315-317 (1993).
29 Biederman, J., Keenan, K. & Faraone, S. V. Parent-based diagnosis of attention deficit disorder predicts a diagnosis based on teacher report. *Journal of the American Academy of Child & Adolescent Psychiatry* **29**, 698-701 (1990).
30 de Nijs, P. F. *et al.* Attention-deficit/hyperactivity disorder (ADHD): parents' judgment about school, teachers' judgment about home. *European child & adolescent psychiatry* **13**, 315-320 (2004).

31 Whalen, C. K., Henker, B. & Dotemoto, S. Methylphenidate and hyperactivity: Effects on teacher behaviors. *Science* **208**, 1280-1282 (1980).

32 Bussing, R., Gary, F. A., Mills, T. L. & Garvan, C. W. Parental explanatory models of ADHD. *Social psychiatry and psychiatric epidemiology* **38**, 563-575 (2003).

33 Ahmann, P. A., Waltonen, S. J., Theye, F. W., Olson, K. A. & Van Erem, A. J. Placebo-controlled evaluation of Ritalin side effects. *Pediatrics* **91**, 1101-1106 (1993).

34 Barkley, R. A., McMurray, M. B., Edelbrock, C. S. & Robbins, K. Side effects of metlyiphenidate in children with attention deficit hyperactivity disorder: a systemic, placebo-controlled evaluation. *Pediatrics* **86**, 184-192 (1990).

35 Offord, D. R. *et al.* Integrating assessment data from multiple informants. *Journal of the American Academy of Child & Adolescent Psychiatry* **35**, 1078-1085 (1996).

36 Bruchmüller, K., Margraf, J. & Schneider, S. Is ADHD diagnosed in accord with diagnostic criteria? Overdiagnosis and influence of client gender on diagnosis. *Journal of consulting and clinical psychology* **80**, 128 (2012).

37 Rucklidge, J. J. Gender differences in attention-deficit/hyperactivity disorder. *Psychiatric Clinics of North America* **33**, 357-373 (2010).

38 Biederman, J. & Faraone, S. V. The Massachusetts General Hospital studies of gender influences on attention-deficit/hyperactivity disorder in youth and relatives. *Psychiatric Clinics of North America* **27**, 225-232 (2004).

39 Gaub, M. & Carlson, C. L. Gender differences in ADHD: a meta-analysis and critical review. *Journal of the American Academy of Child & Adolescent Psychiatry* **36**, 1036-1045 (1997).

40 Biederman, J. *et al.* Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. *American Journal of Psychiatry* **159**, 36-42 (2002).

41 Arcia, E. & Conners, C. K. Gender differences in ADHD? *Journal of Developmental and Behavioral Pediatrics* (1998).

42 Bauermeister, J. J. *et al.* ADHD and gender: are risks and sequela of ADHD the same for boys and girls? *Journal of Child Psychology and Psychiatry* **48**, 831-839 (2007).

43 Breen, M. J. Cognitive and behavioral differences in ADHD boys and girls. *Journal of Child Psychology and Psychiatry* **30**, 711-716 (1989).

44 Derks, E. M., Hudziak, J. J. & Boomsma, D. I. Why more boys than girls with ADHD receive treatment: a study of Dutch twins. *Twin Research and Human Genetics* **10**, 765-770 (2007).

45 Silverthorn, P., Frick, P. J., Kuper, K. & Ott, J. Attention deficit hyperactivity disorder and sex: A test of two etiological models to explain the male predominance. *Journal of Clinical Child Psychology* **25**, 52-59 (1996).

46 Balint, S. *et al.* Attention deficit hyperactivity disorder (ADHD): gender-and age-related differences in neurocognition. *Psychological medicine* **39**, 1337-1345 (2009).

47 Faraone, S. V. *et al.* Genetic heterogeneity in attention-deficit hyperactivity disorder (ADHD). *Journal of Abnormal Psychology* **104**, 334-345 (1995).

48 Biederman, J., Faraone, S. V. & Monuteaux, M. C. Differential effect of environmental adversity by gender: Rutter's index of adversity in a group of boys and girls with and without ADHD. *American journal of psychiatry* **159**, 1556-1562 (2002).

49 Greene, R. W. *et al.* Social impairment in girls with ADHD: patterns, gender comparisons, and correlates. *Journal of the American Academy of Child & Adolescent Psychiatry* **40**, 704-710 (2001).

50 Soldin, O. P., Chung, S. H. & Mattison, D. R. Sex differences in drug disposition. *BioMed Research International* **2011** (2011).

51 Rucklidge, J. J. Gender differences in ADHD: implications for psychosocial treatments. *Expert Review of Neurotherapeutics* **8**, 643-655 (2008).

52 Storebø, O. J. *et al.* Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *The Cochrane Library* (2015).

53 Havey, J. M., Olson, J. M., McCormick, C. & Cates, G. L. Teachers' perceptions of the incidence and management of attention-deficit hyperactivity disorder. *Applied Neuropsychology* **12**, 120-127 (2005).

54 Reid, R. *et al.* Gender and ethnic differences in ADHD as assessed by behavior ratings. *Journal of Emotional and Behavioral Disorders* **8**, 38-48 (2000).

55 Dunn, P. B. & Shapiro, S. K. Gender differences in the achievement goal orientations of ADHD children. *Cognitive therapy and Research* **23**, 327-344 (1999).

56 Abikoff, H. B. *et al.* Observed classroom behavior of children with ADHD: Relationship to gender and comorbidity. *Journal of abnormal child psychology* **30**, 349-359 (2002).

57 Curtis, D. F., Pisecco, S., Hamilton, R. J. & Moore, D. W. Teacher perceptions of classroom interventions for children with ADHD: A cross-cultural comparison of teachers in the United States and New Zealand. *School Psychology Quarterly* **21**, 171 (2006).

58 Batzle, C. S., Weyandt, L. L., Janusis, G. M. & DeVietti, T. L. Potential impact of ADHD with stimulant medication label on teacher expectations. *Journal of Attention Disorders* **14**, 157-166 (2010).

59 DuPaul, G. J. Parent and teacher ratings of ADHD symptoms: psychometric properties in a community-based sample. *Journal of Clinical Child and Adolescent Psychology* **20**, 245-253 (1991).

60 Davis, C. *et al.* The suppression of appetite and food consumption by methylphenidate: the moderating effects of gender and weight status in healthy adults. *International Journal of Neuropsychopharmacology* **15**, 181-187 (2012).

61 Antrop, I., Roeyers, H., Oosterlaan, J. & Van Oost, P. Agreement between parent and teacher ratings of disruptive behavior disorders in children with clinically diagnosed ADHD. *Journal of Psychopathology and Behavioral Assessment* **24**, 67-73 (2002).

13. Appendix 1: Glossary of Terms Used in this Thesis

1. Attention Deficit Hyperactivity Disorder (ADHD)

2. Body Mass Index (BMI)

3. Child Behavior Checklist (CBCL)

4. Clinical Global Index Clinician (CGI-I)

5. Conner's Global Index, Teachers (CON-T)

6. Conner's Global Index Parents (CON-P)

7. Conner's Performance Task (CPT)

9. Decreased appetite

10. Emotional- labile Dimension (EL); Restless Impulsive Dimension (RI)

11. Gender

12. Insomnia

13. Intelligence Quotient (IQ)

14. Methylphenidate (MPH)

15. Observation settings (parents, teachers, objective, clinical)

16. Therapeutic Response (TR)

17. Side Effects (SE)

18. Pharmaco-behavioral study

19. Placebo

20. Randomized Controlled Trial (RCT)

21. Repeated measures analysis of variance (ANOVA)

22. Restricted Academic Situation Scale (RASS)