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ORIGINAL CONTRIBUTION

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Heterogeneity in the pharmacodynamics of two long-acting methylphenidate formulations for children with attention deficit/hyperactivity disorder

A growth mixture modelling analysis

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Abstract *Objectives* To use growth mixture modelling (GMM) to identify subgroups of children with attention deficit hyperactive disorder (ADHD) who have different pharmacodynamic profiles in response to extended release methylphenidate as assessed in a laboratory classroom setting. *Methods* GMM analysis was performed on data from the COMACS study (Comparison of Methylphenidates in the Analog Classroom Setting): a large (n = 184) placebo-controlled cross-over study comparing three treatment conditions in the Laboratory School Protocol (with a 1.5-h cycle of attention and deportment assessments). Two orally administered, once-daily methylphenidate (MPH) bioequivalent formulations [Metadate CD™/ Equasym™ XL (MCD-EQXL) and Concerta XL (CON)] were compared with placebo (PLA). *Results* Three classes of children with distinct severity profiles in the PLA condition were identified. For both MCD-EQXL and CON, the more severe their PLA symptoms the better, the children's response. However, the formulations produced different growth curves by class, with CON having essentially a flat profile for all three classes (i.e. no effect of PLA severity) and MCD-EQXL showing a marked decline in symptoms immediately post-dosing in the two most severe classes compared with the least severe. Comparison of daily doses matched for immediate-release (IR) components accounted for this difference. *Conclusion* The results suggest considerable heterogeneity in the pharmacodynamics of MPH response by children with ADHD. When treatment response for near-equal, bioequivalent daily doses the two formulations was compared, marked differences were seen for children in the most severe classes with a strong curvilinear trajectory for MCD-EQXL related to the greater IR component.

Key words
pharmacodynamics – pharmacokinetics – attention deficit/hyperactivity disorder – stimulant medication – methylphenidate – COMACS – growth mixture models

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Introduction

Methylphenidate (MPH) is an effective treatment [23] for attention deficit/hyperactivity disorder. The pharmacodynamics of MPH (i.e. across-the-day changes in treatment response) has become a focus of major interest following the development of different controlled-release formulations with particular drug delivery and pharmacokinetic profiles [3, 20]. Pharmacodynamic analysis has been facilitated by the development of a specially designed Laboratory School Protocol that allows the systematic measurement of symptoms at multiple points across the day following drug administration in the morning [18, 21].

Standard pharmacodynamic assessment is based on a comparison of change in response for all subjects in a group across different times of the day: this approach assumes that an individual's response trajectory is best characterised as being a member of a single and coherent group of subjects (or latent pharmacodynamic class). However, we know from clinical practice and effectiveness trials that, while MPH is effective in the majority of cases, there are significant variations between patients in their individual treatment responses that require individualisation of dose and dosing regimen [9, 25]. Thus, while many children have a good response to MPH, a minority of children do not respond favourably and the response of most children is less than optimal [10]. This observation leads us to ask: do variations in MPH response exist at the level of individuals' pharmacodynamic profiles in addition to these well-recognised differences in gross measures of symptoms aggregated across the whole day? It would certainly be clinically useful to know whether, for instance, the symptoms of ADHD are greater in the morning or the afternoon [2], or whether there are children who respond better in the morning than the afternoon, or vice versa. This has not been explored sufficiently in the literature to date.

There are a number of different ways of studying this issue. For instance, one might define a particular pharmacodynamic trajectory on an a priori basis (e.g. with a positive morning response relative to an afternoon response) and compare this profile with other pre-defined pharmacodynamic profiles in terms of clinical characteristics. An alternative empirically based approach to identifying pharmacodynamic subtypes is to use the relatively new statistical technique of growth mixture modelling (GMM) [12]. The objective of GMM is to identify whether, within a large group of subjects, heterogeneity exists in how subjects change over time. Put another way, instead of one homogeneous group, GMM asks if the data support the existence of two or more subgroups of individuals—latent classes (LCs)—with different trajectories of change over time. If so, the task is to identify the smallest number of LCs with distinct trajectories. GMM has been used successfully in developmental psychopathology research in a range of settings [24]; however, the application of GMM in the past has been limited to analyses of trajectories over relatively long time scales (months and years; e.g., Cuijpers et al. [7]). GMM is also well suited to the assessment of heterogeneity in treatment response over an hour-by-hour time scale, as is the case with pharmacodynamic analyses of MPH response described in this paper.

In GMM the trajectory of change over time for each individual participant is decomposed into its growth parameters (i.e. intercept, linear, quadratic, etc.). Standard fit indices, in addition to more subjective criteria, are then used to compare models with different numbers of LCs in order to decide upon the optimal solution. GMM has most leverage in terms of identifying valid LCs within a heterogeneous group of trajectories if variation within one condition can be partitioned in terms of performance under a second, more or less independent, condition. In this sense, a randomised placebo (PLA)-controlled trial provides a good vehicle for GMM analyses of MPH pharmacodynamic response, where the heterogeneity in response to MPH can be partitioned in terms of LCs identified by patterns of response growth (change over time) in the PLA condition.

Here we utilise already existing data from the large-scale head-to-head COMACS study (Comparison of Methylphenidates in the Analog Classroom Setting [19]) of two controlled-release MPH formulations [Metadate CD™/Equasym™ XL (MCD-EQXL) and Concerta (CON)]. CON tablets were designed to replace thrice-daily immediate-release (IR) MPH, providing up to 12-h symptom coverage, with 22% of the dose in an IR overcoat and 78% in the extended-release (ER) core. MCD-EQXL capsules were designed to replace twice-daily (b.i.d.) regimes of IR MPH and provide up to 8-h coverage with a ratio of 30% IR to 70% ER MPH beads. Although each formulation results in essentially the same overall systemic exposure, as evidenced by a comparative area under the plasma concentration time curve (AUC), when administered at similar daily doses, the different delivery profiles of the two formulations result in distinctly different pharmacokinetic profiles [8]. In COMACS, as predicted by these pharmacokinetic profiles, MCD-EQXL produced a greater response up to 6 h from drug administration, which was attributed to the 50% larger IR MPH component versus CON for near-equal daily doses. CON produced superior control in the early evening (i.e. at 12 h post-dosing [16, 19]).

The COMACS data set provides a particularly good basis for a GMM analysis of pharmacodynamic heterogeneity for a number of reasons. First, it has a large sample that could provide the statistical power necessary to compare the characteristics of individuals within subsets of participants identified from the sample in terms of their membership of different growth classes. Secondly, it includes data derived from observations of response by trained observers across significant parts of the day, with the number of observations ($n = 7$) being sufficient to allow a range of different growth parameters to be estimated (e.g. from linear to cubic). Thirdly, this trial was designed to provide a within-subject comparison of both formulations against PLA and thus provided the opportunity to assess heterogeneity in response to each formulation using the growth classes of the PLA response condition—a common point of reference for the analysis. Using the PLA condition in this way also allows an indirect assessment of the role of severity after a week of drug withdrawal (at least as modelled using time-series data from the PLA condition in a laboratory classroom, where severity is measured by ratings of attention and deportment on the Swanson, Kotkin, Atkins, M-Flynn, Pelham [SKAMP] rating scale). Severity, along with gender, seems to be one of only a small number of characteristics that are important for prediction of MPH response [16]. Therefore, severity may be an important clinical consideration to guide choices between formulations with different dosing profiles. The current analysis represents the first attempt to model severity using time-series data.

The aims of this re-analysis of the COMACS data, therefore, were to: (i) employ GMM to identify whether there are multiple growth trajectories within the group in the PLA condition and (ii) use the derived latent growth classes (subgroups) to partition variations in pharmacodynamic profiles following a morning dose of MCD-EQXL and CON. The clinical and background characteristics (titrated dose or strata, severity, ADHD subtype status, comorbidity, gender, etc.) of the individuals within the different growth classes will also be compared, and any differences between groups will be controlled in the comparison of the pharmacodynamic profiles of the two MPH formulations.

Methods

Patients

Six- to 12-year-old children, receiving treatment with doses of MPH between 10 and 60 mg/day (5–20 mg per administration, one to three times a day) were recruited for the multi-site COMACS trial. The subjects were screened and enrolled by the principal investigator at each study site (Appendix 1). Children were deemed otherwise healthy on the basis of an extensive medical history and physical examination; diagnosis of ADHD was confirmed by a clinical research interview carried out by a trained interviewer. Children were excluded if they had an IQ below 80 or the inability to follow or understand study instructions. Other exclusion criteria included severe mental disorder (e.g. psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, or severe depressive disorder), extreme aggressive behaviour or destruction of property, marked anxiety, tension, or agitation. Comorbid psychiatric diagnoses were established at the screening visit by reference to DSM-IV criteria (see Swanson et al. [22] for details). A total of 184 patients (48 female) entered the trial. Eighty-two percent of the patients met criteria for ADHD-combined type, 15% met criteria for inattentive type, and the remaining 3% met criteria for hyperactive/impulsive type. Approximately 25% of the children had a comorbid condition (e.g., anxiety and oppositional defiant disorder). At prescreening, 9% of the patients were on once-a-day dosing regimens with extended release MPH preparations: 54% on the t.i.d. equivalent formulation of CON and 23% on the b.i.d. equivalent formulation of MCD-EQXL. Of the remainder, 7.6% were taking b.i.d. IR MPH and 1.6% t.i.d. IR MPH. The current analysis was based on 169 patients who participated in all three treatment conditions. The 15 cases not included in the sample were slightly younger, $F(1, 183) = 7.067$, $P < 0.01$, and were more likely to have a co-morbid anxiety disorder χ^2 $(1, n = 185) = 4.65$, $P < 0.05$, when compared with the rest of the group.

Design

COMACS was a 10-site, double-blind, placebo-controlled, cross-over study comparing three treatment conditions: MCD-EQXL, CON and PLA. Dose-level assignment was made according to the pre-study, clinically titrated daily dosing regimen for MPH and remained at that level for the study duration. Children treated with low doses (≤20 mg/day) of MPH were randomised to receive a daily dose of MCD-EQXL 20 mg, CON 18 mg or PLA; those treated with medium doses (>20–40 mg/day) were randomised to receive MCD-EQXL 40 mg, CON 36 mg or PLA; and children treated with high doses (>40 mg/day) were randomised to receive MCD-EQXL 60 mg, CON 54 mg or PLA. Each of the three treatments was administered for 7 days (in the assigned sequence) without an intervening washout period, and the pharmacodynamic assessment was conducted on the seventh day of each treatment.

Assessment

Assessment took place in the laboratory school on days 7, 14 and 21 (for a detailed description of the laboratory classroom facility see [17, 21, 22, 26]). Two trained observers assessed patients during each classroom session on the Swanson, Kotkin, Atkins, M-Flynn, Pelham (SKAMP) scale on the basis of a 1.5-h cycle of activities, with separate assessments of attention and deportment being made at 0 (i.e., predose or baseline), 1.5, 3.0, 4.5, 6.0, 7.5 and then 12 h after drug administration. The laboratory classroom scores (SKAMP and PERMP) were completed by dedicated raters at each study site. These raters were required to complete pre-study standardisation training administered by UCI staff; however, the inter-rater reliability was not formally assessed.

The SKAMP has six deportment items (e.g. staying seated, interacting with others) and seven attention items (e.g. getting started, sticking with tasks). Parents of the children also completed the Swanson, Nelson & Pelham scale (version IV; [17]), which has 39 items derived from the Diagnostic and Statistical Manual (DSM) criteria for ADHD and ODD. The items on this scale are reproduced from DSM-IV and DSM-III symptoms for ADHD. Parents and teachers respond on a Likert scale rating the presence of these symptoms. Making use of only the DSM-IV symptoms, the scale yields ADHD-related factor scores for inattention and hyperactivity–impulsivity.

Statistical approach

The pharmacodynamics of MCD-EQXL and CON was studied through two stages. First, the repeatedly assessed ADHD symptom scores during PLA were used to determine the optimal number of distinct subgroups of children through GMM. As described above, the objective was to determine the smallest number of subgroups—or latent classes (LCs)—of children with distinct across-day courses of attention and deportment. Three criteria are used to determine the optimal number of LCs. The first is a low Bayesian information criterion (BIC) [11]. Lower BIC values indicate a better fit of the model with N LCs when compared with the $N - 1$ LC model. The second is the usefulness of the LCs, which involves the subjective interpretation of the developmental course of the trajectories, and the number of children in each LC. The third is the stability of the model. This was tested through the use of different starting values. For each model, 200 random perturbations of starting values were generated by the program. A model is stable when, despite different starting values, similar solutions are obtained. As long as the usefulness and stability criteria are met, the model with the lowest BIC value is considered the optimal solution. The outcomes of the trajectory model are LC membership probabilities, which give the probabilities of an individual belonging to each of the LCs, and the means and variances of the growth parameters.

The LC membership probabilities were essential for the second phase of analysis. A child with a high severity profile across the day would have a high probability of belonging to a high LC but a low probability of belonging to a low LC. In the second phase, we estimated the impact of MCD-EQXL and CON on the responses of children in each of the identified PLA LCs. A multiple group GMM model (e.g., MCD-EQXL versus CON) was run in which the response curves of children under MCD-EQXL and CON medication were compared. The Satorra scaled log-likelihood difference test [14] was used to determine any significant differences between the pharmacodynamic trajectories of response across the day for children within each of the LCs under different conditions (e.g. MCD-EQXL versus CON). The class membership probabilities are included in the model to identify the children in each of the classes. All analyses were performed with Mplus 4.2 [13]. Differences between the formulations in the time-course of response across the day were tested using analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA) models. In these analyses, all differences between LCs in background and clinical factors were entered as covariates.

Results

Identifying the optimal number of classes

To determine the number of growth parameters needed to model the repeated assessments across the day in the PLA condition, models with up to four growth parameters (intercept, linear growth term, quadratic growth term, cubic growth) were fitted. The comparative fit index (CFI) and the Tucker Lewis index (TLI), which take the parsimoniousness of the model and sample size into account, were used to determine model fit [4, 5]. Values >0.90 are considered an adequate fit. Using these criteria, the final model with four growth parameters (intercept, linear, quadratic and cubic growth terms) had a good fit to the data: CFI = 0.96, TLI = 0.97.

We then determined the optimal number of LCs. Initially, the growth factor variances and covariances were set to zero, while the variances of the repeatedly assessed severity scores were held equal over time. LC-specific variances/covariances were not used in this phase of analysis. GMM analyses re-

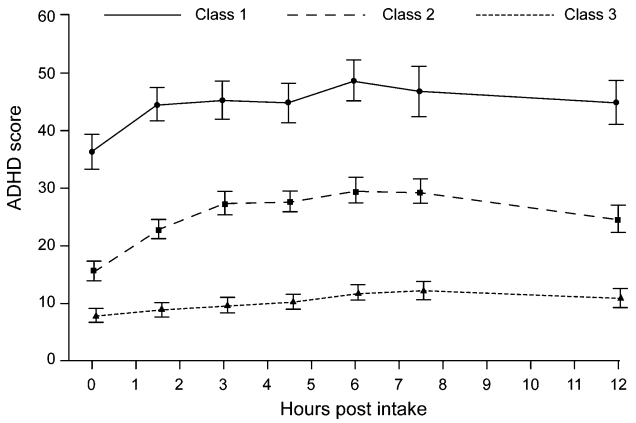

Fig. 1 Across the day trajectories for the three latent growth classes derived using growth mixture modelling of across-day ADHD symptoms for children under the placebo condition. Values are means ± standard error. The numbers in each class are: high = 23, intermediate = 75, low = 71 children

vealed a gradual improvement in the fit of the model with an increase from one to four LCs (BIC 1 LC = 9,504; BIC 2 LC = 8,794; BIC 3 LC = 8,393; BIC 4 LC = 8,284). Using five or more LCs resulted in the addition of small LCs with children with low severity (not meeting the usefulness criterion) or in unstable or non-converging solutions. We then allowed for variances in the growth parameters and LC-specific variances for the three- and four-LC solutions. The optimal three-LC solution, with LC-specific variances in a low severity LC and variances on the intercept and linear term, had a BIC value of 8,123. The BIC of the optimal four-LC solution was 8,135. We therefore judged that the across-day course of response was best described by three distinct trajectory classes of children.

Classes of PLA ADHD symptom curves

The mean severity levels at each measurement point during the day for each LC are shown in Fig. 1. Although different in other growth parameters, these LCs were characterised most easily by difference in intercept or the overall severity. Twenty-three children (12.4%) were in a high severity LC, 75 (40.5%) in an intermediate severity LC and the remaining 71 (38.4%) in a low severity LC. The characteristics of children in each of the three severity LCs are presented in Table 1. There was also an effect of site on LC membership, with children in the low symptom category being especially likely to come from two of the study sites. In the original analyses of COMACS, these two sites were dropped, but the results did not change from the results of the analysis including all sites [22]. Therefore, all sites were included in the current analysis of individual differences in MPH response. The LCs did not differ in average titrated dose level. Individuals in the high severity LC tended to have diagnoses of ADHD-combined type and be male, with an intermediate level of comorbidity. Those in the intermediate severity LC tended also to have diagnoses of ADHD-combined type and be male, but had the highest level of comorbidity. The individuals in the low severity LC were most likely to be female, older in age and have a diagnosis of ADHD-predominantly inattentive type rather than ADHD-combined type, and very low levels of comorbidities. Interestingly, this low severity LC did not differ from the other two LCs in terms of ratings of symptoms of ADHD in the natural environment of the home and school. This suggests that, on average, subjects in all LCs had equal severity of symptoms of ADHD in their normal or everyday lives.

Table 1 Age, gender, ADHD subtype and comorbid ODD and anxiety for children in the 3 day-time ADHD latent classes

	ADHD latent class			Test	
	High (N = 23)	Intermediate (N = 75)	Low (N = 71)	Statistic	df
Age	9.00 (2.20)	9.45 (1.78)	10.17 (1.45)	F = 5.30**	2,166
Male sex (%)	82.6	81.3	62.0	χ^2 = 8.16**	2
Dose level (% high)	15.1	47.2	37.7	χ^2 = 2.57	4
ADHD symptoms					
SNAP inattention	1.26 (0.39)	1.34 (0.51)	1.21 (0.47)	F = 1.24	2,166
SNAP hyperactive	1.29 (0.44)	1.24 (0.64)	1.05 (0.49)	F = 2.85	2,166
Subtype ADHD (%)				χ^2 = 16.21**	4
Combined	87.0	93.3	69.0		
Inattentive	8.7	6.7	22.5		
Hyperactive/imp	4.3	0.0	8.5		
Comorbidity (%)					
ODD	8.7	16.0	1.4	χ^2 = 9.60**	2
Anxiety	4.3	14.7	2.8	χ^2 = 7.28*	2

Values in parenthesis are standard deviations
ADHD = attention deficit hyperactivity disorder; ODD = oppositional defiant disorder
* $P < 0.05$, ** $P < 0.01$

MCD-EQXL and CON pharmacodynamics for children in each of the PLA growth classes

We then compared the MPH pharmacodynamics for the two formulations (MCD-EQXL versus CON) for each of the three identified LCs. The means and standard errors of the across-the-day response profiles for each to the three conditions (PLA, MCD-EQXL and CON) are plotted in Fig. 2 for children in each class separately. Differences between MCD-EQXL and CON were observed in terms of the shape of the growth curves. CON had essentially a flat profile for all three LCs, with little difference in severity at different times of the day. While this was true for MCD-EQXL for the patients in the low severity LC (due perhaps to the negligible overall effect), for those in the intermediate and high severity LCs the growth trajectory followed a cubic function with a marked decline in severity immediately post-dosing relative to CON.

While the visual interpretation of the trajectories suggests possible differences between the two MPH formulations, it is important to test whether these pharmacodynamic differences are statistically significant. We performed a number of tests to investigate this. We first tested whether the trajectories for the three conditions were different from each other by holding the four growth parameters (intercept, linear, quadratic and cubic term) equal between conditions for each of the three LCs (i.e. assuming that the within-day course of ADHD symptoms were similar across conditions). The results shown in Table 2 suggest that for each of the three classes the curves reflecting the MPH pharmacodynamic for MCD-EQXL and CON were both different from PLA (see Table 2, first and second row). When comparing near-equal daily doses of MCD-EQXL and CON with each other (see Table 2, third row), significant differences in the growth parameters were again found. This indicates that the time–response curves were statistically different from one another in terms of the linear, quadratic and cubic parameters. These effects remained when other factors that distinguished the membership of LCs (age, gender, etc.) were controlled using analysis of covariance (ANCOVA).

To evaluate which assessment times were responsible for these observed differences, a MANOVA was conducted (controlling for age, sex, ADHD subtype and comorbid ODD and anxiety). For each of the three classes significant time-of-day × condition interactions were found: $F_{(14,\ 98)} = 4.55$, $P < 0.01$ for the high severity class; $F_{(14,\ 410)} = 15.46$, $P < 0.01$ for the intermediate severity class; $F_{(14,\ 396)} = 5.15$, $P < 0.01$ for the low severity class. Means (SDs) and post-hoc tests and between the observed severity scores at each time-point are in Table 3. The results mainly underscore that for near-equal daily doses, MCD-EQXL is superior to CON in response early in the day, soon after administering the drug in the high and intermediate severity LCs. The predicted superiority for CON at the 12-h point was present only for

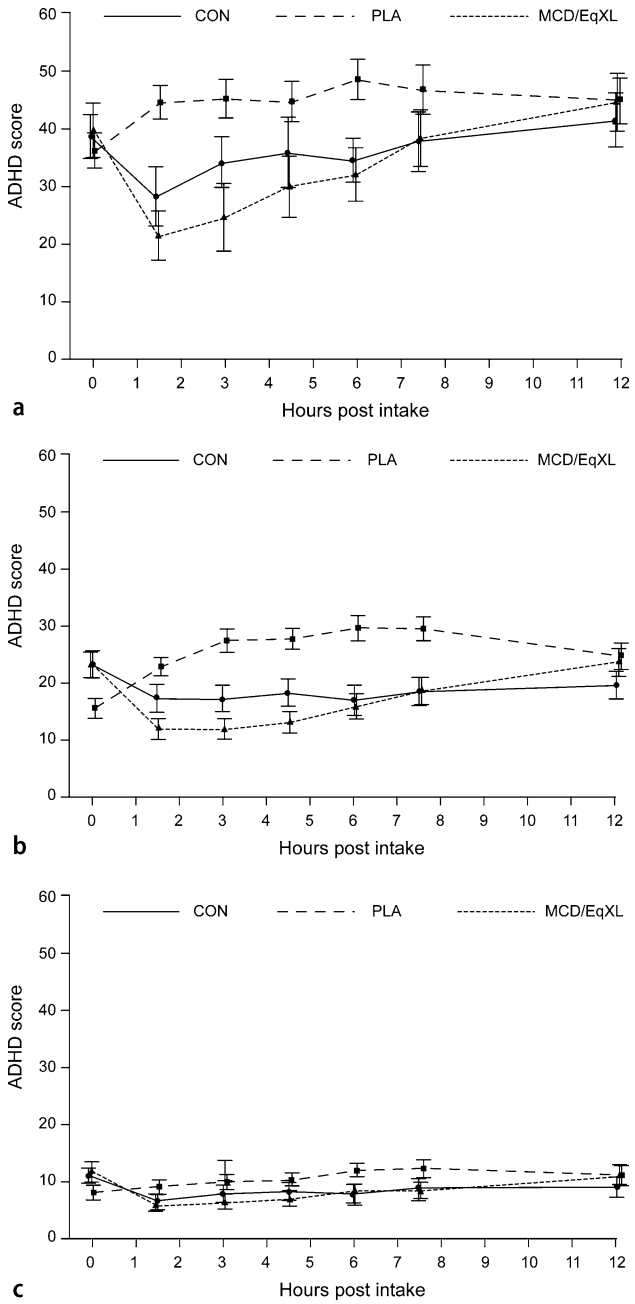

Fig. 2 (**a**–**c**) Across-day ADHD symptoms for PLA, CON and MCD-EQXL for children in the three placebo latent growth classes. Values are means ± standard error. The numbers in each class are: high = 23, intermediate = 75, low = 71 children

Table 2 Test statistics (−2 log-likelihood) for holding growth parameters of day curve ADHD symptoms equal between conditions, for the three ADHD classes separately

	Class		
	High	Intermediate	Low
PLA versus CON	49.97**	138.30**	45.58**
PLA versus MCD-EQXL	109.63**	188.64**	42.02**
CON versus MCD-EQXL	20.96**	42.09**	12.07*

Entries represent −2 log-likelihood difference statistics with four degrees of freedom
* $P < 0.05$, ** $P < 0.01$

the intermediate severity LC. The sizes of these effects are mainly in the medium–large range [6].

This study used a non-equivalence design to compare the two formulations at near-equal daily doses that were bioequivalent by usual regulatory standards (i.e. resulted in equal overall levels of exposure to MPH across the day). When equated in this way, the formulations differ markedly in terms of the relative size of the IR component. The absolute difference between IR components of the formulations (in mg) is small, and only small differences in response were expected, so a large sample was required by the COMACS design. However, at these near-equal doses, MCD-EQXL has 50% more IR MPH in the initial bolus delivery process than CON (6 vs. 4 mg at the low daily dose, 12 vs. 8 mg at the medium daily dose and 18 vs. 12 mg at the high daily dose), but the same amount of extended release MPH (for both MCD-EQXL and CON, 14 mg at the low, 28 mg at the medium or 42 mg at the high daily doses). In order to test whether the morning advantage of MCD-EQXL in response was due solely to these differences in the IR component, as suggested by post-hoc analyses in the initial COMACS report [22], we conducted a supplementary cross-dose analysis in which we attempted to control for the IR component of the two formulations. This was achieved by restricting analyses to the data from the conditions when children were given low and medium doses of MCD-EQXL (with IR components of 6 and 12 mg, respectively) and medium and high doses of CON (with IR components of 8 and 12 mg, respectively), which have near-equal IR components. In order to maintain statistical power, children from the intermediate and high severity LCs were combined for this secondary analysis. The findings are shown in Fig. 3. IR dose was not related to the revised trajectory group membership: χ^2 (4, $n = 226$) = 3.56, $P > 0.05$. ANOVA showed that differences between the high/medium dose of CON and the medium/low

Table 3 Means and standard deviations of across the day SKAMP symptom scores for children in the high, intermediate and low latent classes

	PLA		CON		MCD-EQXL		Effect size		
Time (h)	M	SD	M	SD	M	SD	MCD/PLA	CON/PLA	MCD/CON
High class									
0	36.22^a	7.32	38.65^a	9.08	39.75^a	11.49	–	–	–
1.5	44.52^a	6.98	28.22^b	12.37	21.52^c	10.35	2.61	1.62	0.59
3.0	45.23^a	7.86	34.22^b	10.55	24.68^c	14.09	1.80	1.18	0.77
4.5	44.69^a	8.35	35.90^b	14.28	30.02^b	12.91	1.35	0.75	–
6.0	48.57^a	8.44	34.61^b	9.37	32.13^b	11.05	1.67	1.57	–
7.5	46.75^a	10.13	37.74^b	12.61	38.39^b	11.88	0.76	0.79	–
12	44.83^a	8.94	41.50^a	11.09	44.59^a	11.78	–	–	–
Intermediate class									
0	15.55^a	7.81	23.11^b	9.71	23.20^b	10.53	0.83	0.86	–
1.5	22.87^a	7.21	17.32^b	10.79	11.89^c	7.65	1.48	0.60	0.58
3.0	27.31^a	8.97	17.19^b	9.97	11.93^c	7.46	1.86	1.07	0.60
4.5	27.69^a	7.80	18.24^b	10.14	13.12^c	8.66	1.77	1.04	0.54
6.0	29.57^a	7.13	16.91^b	11.49	15.89^b	9.56	1.62	1.32	–
7.5	29.43^a	9.21	18.46^b	10.67	18.59^b	10.36	1.11	1.10	–
12	24.62^a	10.16	19.61^b	10.82	23.62^a	10.68	–	0.48	0.37
Low class									
0	7.91^a	5.15	10.93^b	5.36	11.65^b	7.28	0.59	0.57	–
1.5	8.88^a	5.24	6.59^b	4.76	5.66^b	4.48	0.66	0.46	–
3.0	9.69^a	5.71	7.65^b	6.12	6.20^b	4.98	0.65	0.34	–
4.5	10.24^a	5.19	8.08^b	6.70	6.77^b	5.57	0.64	0.36	–
6.0	11.87^a	5.52	7.80^b	6.62	8.27^b	10.10	0.44	0.67	–
7.5	12.21^a	6.63	8.56^b	8.04	8.21^b	5.56	0.65	0.50	–
12	10.92^a	7.00	8.90^a	7.58	10.94^a	7.64	–	–	–

M = means, SD = standard deviation
Different superscript letters within rows indicate significant different means SKAMP symptom scroes between treatment condition (PLA, CON, MCD-EQXL), using LCD correction for multiple testing. Only significant effect sizes are shown ($P < 0.05$)

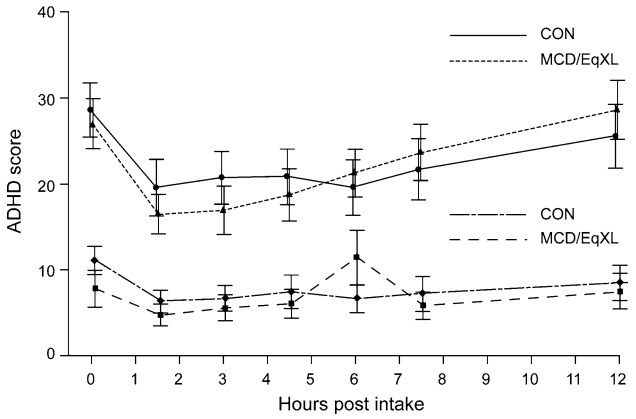

Fig. 3 Across-day ADHD symptoms for CON and MCD-EQXL, controlled for IR dose, for children in the high/intermediate (combined) and low latent growth classes. Values are means ± standard error. The numbers in the two groups were: intermediate combined = 98 (23 + 75) children, low = 71 children

dose of MCD-EQXL formulations at any time-point for either of the groups of children failed to reach significance ($F_{<2.37}$; $P = 0.125$).

Conclusion

This paper provides the first application of GMM to explore heterogeneity in the pharmacodynamics of MPH in ADHD. Overall, the results support the value of GMM in the analysis of time-series data on the pharmacodynamic of MPH response as measured in the Laboratory School Protocol. There are a number of new insights provided by this novel approach. First, and most generally, the analyses suggest that the pharmacodynamic responses of individual patients to MPH (at least in the COMACS study) may not be best modelled as a single homogeneous group but rather as three distinct subgroups (LCs), differing systematically from each other in terms of a number of different characteristics. One subgroup of children has low levels of severity manifested in the laboratory classroom across the day in the PLA condition, and children in this subgroup are more likely to be older, female and diagnosed with ADHD-predominantly inattentive type with low levels of comorbidity. This group shows a rather flat pharmacodynamic profile on both MPH formulations, suggesting that while both had a significant effect on symptoms, these effects were much smaller in size than for the other two subgroups (LCs), as would expected given their already low levels of severity in the laboratory classroom. A second LC had a moderate level of severity and a growth curve marked by quadratic and cubic growth parameters. This LC tended to contain more complex and comorbid cases than either of the other two classes. Members of this LC showed a larger response to MPH in general than was shown by the members of the low severity LC; there was also a marked differentiation between the two formulations, with MCD-EQXL showing an initial superiority to CON at 1.5–4.5 h post-drug intake, but the opposite being the case at 12 h post-intake. The final class was marked by the highest severity at baseline (time zero) on the PLA day of the trial, which increased further over the laboratory school day. This high severity subgroup (LC) showed the largest treatment effects relative to PLA. A comparison across LCs revealed that the difference in pharmacodynamic profiles for the two formulations increase with severity of the LC, due to CON having a similar flat profile for all three LCs, while MCD-EQXL superiority in the morning increased with severity that defined the LCs. The reasons for these different effects of pharmacodynamic response to MPH as a function of LC require further investigation. To test whether this difference in reduction in ADHD symptoms was due to differences in IR dose between the two drugs, IR dose was equated by removing children on the high MCD-EQXL dose or the low CON dose; some differences at the high levels persisted. When this was conducted, as predicted, there were no significant differences between the two formulations in the early part of the day, even in the combined severe group. This finding highlights the role of the greater IR dose in MCD-EQXL in determining its early morning superiority in the more severe groups seen in the main analysis.

A recent paper reported a significant sex difference in pharmacodynamic in the COMACS study, with girls showing a more intense initial effect and a shorter duration of action for both MPH formulations [16]. At first sight, this result seems to stand in contrast to the current finding, in which girls were most likely to occupy the class that showed the smallest response to MPH in general. However, the results of these two analyses are not comparable. In the gender difference analysis reported previously [16], the effects of sex emerged only after large differences severity at baseline and in the PLA condition were controlled. In the current analysis the gender disparity between the PLA groups was controlled before the efficacy of CON and MCD-EQXL were compared.

Limitations

The current study has a number of limitations. Although COMACS is one of the largest studies using the Laboratory School Protocol ever conducted, the statistical power to explore differences was still relatively low, due to the fractionation of the sample into subgroups of children identified on the basis of their growth class membership. The differences reported

here may underestimate the effects, especially for the high severity subgroup (LC), which was comprised of the lowest number of children. The Laboratory School Protocol employed in the current study employs surrogate measures of children's behaviour set in a specialised environment. The importance of this issue for the current study is highlighted in relation to the subgroup (LC) consisting of participants who displayed low levels of severity within the laboratory classroom on the PLA condition. This was slightly surprising, as all children were assessed rigorously prior to entry into the study and all met the full diagnostic criteria for ADHD; there was no difference between LCs in terms of parents' ratings of symptoms of ADHD outside the laboratory classroom setting. There are at least four possible interpretations of this result: first, that the SKAMP and the SNAP measure different aspects of ADHD symptoms even when used in the same setting and context. Second, that the two sites with especially low SKAMP scores contributed differentially to this group [22]. Third, that the low severity LC were placebo responders—although the fact that the LC differences in severity occurred at time zero just before dosing is not consistent with this view. Fourth, this apparent discrepancy between diagnostic assessment and the low PLA scores is due to the laboratory school setting, with high levels of structure and good staff:student ratio, which was therapeutically beneficial. This could be tested by examining the pharmacodynamic profiles in a more naturalistic setting using repeated measurements of symptoms according to the same time schedule as that used in the laboratory classroom, as suggested by Antrop et al. [2]. The current study had unusually low levels of severe comorbid disorders for an ADHD treatment trial, probably as a result of the exclusion criteria used. The impact of including the most severe, complex cases on the pasterns of heterogeneity and as associated MPH responses could not be established in this study and requires further research.

The design of the COMACS study, and especially the selection of comparator doses for different formulations and release profiles of the same drug, has been a subject of considerable debate. The main issue relates to what are the dosing equivalents for MCD-EQXL and CON. In the COMACS, bioequivalent total daily doses were used as the basis for matching the two formulations, and a non-equivalence design was employed to test for pharmacodynamic differences relating to a small absolute difference in the IR components of the formulations (e.g. 4 vs. 6 mg; 8 vs. 12 mg; 12 vs. 18 mg). An alternative design suggested by Adesman [1] would match formulations based on IR to give a "fair" comparison, but this would require a strategy of accepting the null hypothesis of no difference rather than rejecting the null hypothesis as in the COMACS design [19]. After rejecting the null hypothesis, post-hoc analyses were used to compare doses of the two formulations equated in terms of their IR components (see [15, 19] for discussion). In similar post-hoc analyses reported here, differences in the two formulations in the morning could not be demonstrated, but the sample size may be too small to accept the null hypothesis of non-difference.

Clinical implications

Different patients appear to respond in different ways to extended release MPH formulations in general. This highlights the importance of evaluating individual differences in the pharmacodynamics of MPH response when considering treatment options for children with ADHD. In particular, it appears that for comparison of bioequivalent and near-equal daily doses, children with high levels of severity may benefit particularly from the drug delivery profile of MCD-EQXL with its larger IR component than the drug delivery profile of CON.

How best to assess individual differences in drug response needs careful consideration. In the current study, the subgroups with different response profiles were identified on the basis of performance in the PLA condition in the laboratory classroom and not on the basis of parent or teacher ratings in normal settings. Further research is required to identify more cost-effective ways of assessing individual differences in MPH response that have both predictive power and can be used in everyday clinical practice. Finally, the current analysis highlights the potential role of statistical techniques such as GMM to further our knowledge about subpopulations who may respond more favourably to particular treatments.

Appendix 1

Investigators enrolling patients

Site no.	Name of investigator	Address
01	Joseph Biederman, MD	Massachusetts General Hospital
02	Ann Childress, MD	Nevada Behavioral Health, Inc.
03	Flemming Graae, MD	New York Presbyterian Hospital
04	Laurence Greenhill, MD	New York State Psychiatric Institute
05	Scott Kollins, PhD	Duke Family and Child Clinic
06	Frank Lopez, MD	Children's Developmental Center, Maitland, FL
07	Sharon Wigal, PhD	UCI Child Development Center
10	Eliot Moon, MD	Elite Clinical Trials, Inc.
11	John Turnbow, MD	Behavioral Neurology, Suite A Lubbock
12	Matthew Brams, MD	Bayou City Research, Ltd.

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