Published in final edited form as:

Pediatrics. 2009 July ; 124(1): 226–233. doi:10.1542/peds.2008-1855.

Side Effects of Methylphenidate in Survivors of Childhood Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

OBJECTIVES—To investigate the frequency and severity of side effects of methylphenidate (MPH) among childhood survivors of acute lymphoblastic leukemia (ALL) and brain tumors (BT), and to identify predictors of higher side effect levels.

PARTICIPANTS AND METHODS—Childhood cancer survivors ($N = 103$; BT=54, ALL=49) identified as having attention and learning problems completed a randomized, double-blind, three-week, home cross-over trial of placebo, low-dose MPH (LD; 0.3mg/kg; 10 mg maximum bid) and moderate-dose MPH (MD; 0.6 mg/kg; 20 mg maximum bid). Caregivers completed the Barkley Side Effects Rating Scale (SERS) at baseline and each week during the medication trial. Siblings of cancer survivors ($N = 49$) were recruited as a healthy comparison group.

RESULTS—There was a significantly higher number and severity of symptoms endorsed on the SERS when patients were taking MD compared to placebo or LD ($ps < .001$) but not LD compared to placebo ($p = .143$ and $p = .635$, respectively). The number of side effects endorsed on the SERS was significantly lower during all three home-cross over weeks (placebo, LD, MD) when compared to baseline symptom scores ($ps < .001$). The severity of side effects was also significantly lower, compared to baseline screening, during placebo and LD weeks ($p < .001$ and $p = .003$, respectively), but not MD week ($p = .925$). Both the number and severity of symptoms endorsed at baseline were significantly higher for patients compared to siblings ($p < .001$ and $p = .004$, respectively). Female gender and lower IQ were associated with higher side effect levels ($ps < .05$).

CONCLUSIONS—MPH is generally well tolerated by childhood cancer survivors. There is a subgroup at increased risk for side effects that may need to be closely monitored or prescribed a lower medication dose. The seemingly paradoxical findings of increased “side effects” at baseline must be considered when monitoring side effects and designing clinical trials.

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Publisher's Disclaimer: Disclaimers: This study is registered at clinicaltrials.gov-NCT00576472

Keywords

leukemia; brain tumor; methylphenidate; stimulant; side effects

INTRODUCTION

Childhood survivors of acute lymphoblastic leukemia (ALL) and malignant brain tumors (BT) are at risk for cognitive impairments secondary to their disease and treatment.^{1–3} Stimulant medications, such as methylphenidate (MPH), are among the most effective and safest interventions for child and adolescent attention and behavioral difficulties.⁴ These medications have been used for decades to successfully and safely treat children with attention deficit hyperactivity disorder (ADHD).⁵ There is recently emerging evidence for the efficacy of stimulant medications in improving cognitive impairments among childhood cancer survivors.^{6–8} Establishing the safety of stimulant medications for childhood cancer survivors, in addition to efficacy, is imperative to inform clinical practice. With improved long-term survival rates, the medical care of childhood cancer survivors, including the management of late effects, is increasingly overseen by pediatricians.^{9–10}

The majority of children treated with stimulant medications experience some adverse side effects; these are usually mild to moderate, and dose-dependent.¹¹ For example, reported mean severity ratings have ranged from 0.6 to 2.6 out of 9.0 on the Side Effects Rating Scale (SERS) for 3 mg/kg MPH taken two times daily and 0.8 to 3.1 out of 9.0 for 5 mg/kg MPH taken two times daily.¹² The most common stimulant medication side effects in children with ADHD are decreased appetite, insomnia, headaches, dizziness and stomachaches.¹³ Children who are neurologically compromised may have lowered response rates or tolerance to MPH treatment¹⁴ such that findings in the ADHD literature may not be generalizable to childhood cancer survivors.

The ADHD literature indicates that children with attention difficulties often display what can appear to be MPH “side effects” even *before* receiving stimulant medication.^{12–13, 15–17} These authors maintain that specific side effects (e.g., daydreaming, nailbiting) may actually represent features of the behavioral presentation of ADHD rather than true medication adverse effects.^{13, 15, 16–17} Ascertaining baseline ratings prior to administering a medication or placebo can assist in differentiating symptoms of attention problems from medication side effects.

There is preliminary evidence to suggest some childhood cancer survivors may be at increased risk for MPH side effects.^{7, 18} Mulhern et al. found 9 of 83 patients experienced side effects sufficient to discontinue MPH; 7 of these 9 children had been treated for a BT, even though the sample included equal numbers of BT and ALL patients. DeLong et al. reported anecdotal findings from a study of 12 cancer survivors that indicated children receiving more intensive treatment exhibited a poorer MPH response, sometimes accompanied by marked side effects.¹⁸ There is a clear need to characterize factors that may place childhood cancer survivors at higher risk for MPH side effects in order to increase the specificity of treatment guidelines and improve monitoring for stimulant drug response. In addition, a higher incidence of side effects may contribute to poor treatment compliance, as evidenced by adherence studies with childhood ADHD populations.¹⁹

The current study expands upon the initial qualitative observations of Mulhern et al.⁷ by comparing levels of adverse side effects of cancer survivors participating in a randomized, placebo-controlled, double-blind, cross-over trial of MPH, across low dose (LD) and moderate dose (MD) weeks, relative to placebo and baseline screening. The primary goals of this study

were to investigate the frequency and severity of MPH side effects and identify potential predictors of higher side effect levels. We first hypothesized patients would exhibit higher levels of MPH side effects during both LD and MD weeks compared to placebo. Based on the ADHD literature,^{13, 15, 16–17} our second hypothesis was that patients would exhibit higher “side effect” scores at baseline compared to placebo, LD, and MD weeks as reflective of baseline attention problems. For our third hypothesis we predicted patient baseline “side effect” levels would be higher than those of a sibling comparison group given the patient group is more likely to exhibit attention problems that can inflate side effect ratings. Our fourth hypothesis was that a BT diagnosis and higher treatment intensity would predict higher levels of MPH side effects.⁷

PARTICIPANTS AND METHODS

Participants

The present study is the home cross-over phase of a multi-phase, multi-site MPH trial in childhood cancer survivors for which patient eligibility criteria have been previously described.^{6–8} Briefly, patients were primary English speakers, between the ages of 6 and 18, treated for ALL or a BT with chemotherapy and/or CNS-directed radiation therapy and completed treatment at least 12 months prior to study enrollment with no evidence of recurrent disease. Exclusion criteria included a premorbid ADHD diagnosis, uncontrolled seizures, uncorrected hypothyroidism, severe sensory loss, family history of Tourette syndrome, glaucoma, substance abuse history or current use of psychotropic medications. Siblings were healthy siblings of cancer survivors between 6 and 18 years of age who did not meet the exclusion criteria above. The protocol was approved by the Institutional Review Boards of participating sites [St. Jude Children’s Research Hospital (SJCRH), Duke University Medical Center, and Medical University of South Carolina]. Written informed consent was required from a legal guardian prior to participation. Patient enrollment began in January 2000.

Procedure and Measures

Patients—Potentially eligible patients were contacted via mail or during routine clinic visits. If interested, patients were screened using a battery of psychological tests and parent/teacher report forms. These tests were used to assess whether patients had adequate intellectual functioning and attention and academic difficulties that might be responsive to MPH.⁸ Detailed information on the screening phase has been previously reported.^{6–7}

Qualifying patients participated in a two-day, in-clinic, cross-over trial. They were stratified on the basis of age at CNS treatment (< 4 years and ≥ 4 years) and intensity of CNS therapies (low-systemic and/or intrathecal chemotherapy only, mild- ≤ 24 Gy cranial radiation therapy with or without chemotherapy, and moderate- > 24 Gy cranial radiation therapy with or without chemotherapy) due to differential cognitive risk. They were then randomly assigned by the study pharmacist to either receive MPH (0.60 mg/kg; maximum dose 20 mg) on day 1 and placebo on day 2, or the reverse, in a double-blind design.⁶ Other study personnel were blind to medication order. Patients without severe adverse reactions to MPH during the in-clinic trial proceeded to a randomized, double-blind, placebo-controlled, three-week home cross-over trial of MPH. Severe adverse reactions were defined as scores ≥ 7 on the SERS.

The SERS questionnaire was developed by Barkley to assess the frequency and severity of 17 common adverse side effects of stimulant medication, as rated by parents on a scale from 0 (absent) to 9 (severe).²⁰ This measure has been widely used in studies of stimulant medication in ADHD populations.^{12, 15–17, 19}

For the three-week home-crossover period, each patient was randomly assigned to one of six permutations of placebo, LD and MD by the pharmacist. MD was defined as 0.60 mg/kg (20 mg maximum) bid, and LD was defined as 0.30 mg/kg (10 mg maximum) bid. MPH or placebo was administered five days per week, with a weekend washout period. During the three-week period, parents and teachers completed report forms via telephone calls with the study nurse. The SERS was completed by a caregiver at baseline, during the in-clinic trial, and at the end of each week during the home cross-over trial.

Siblings—Parents of eligible patients were also contacted to recruit a healthy sibling comparison group. Siblings that were eligible and interested were tested using the same battery of psychological tests and parent/teacher report forms as for patients at baseline screening. Caregivers completed the SERS for siblings at baseline.

Clinical Variables

Body mass index (BMI) was gathered from the closest clinic visit to the start of the home cross-over trial. Kidney function was characterized by creatinine levels and liver function by albumin levels, both from closest laboratory results. Medical charts were reviewed to identify patients who underwent placement of a ventriculoperitoneal shunt or a permanent ventriculostomy to manage hydrocephalus.

Statistical Analyses

Descriptive statistics were calculated for demographic and clinical characteristics. For all other analyses, the dependent variables were mean number of side effects endorsed (i.e., total number of symptoms rated greater than 0) and mean severity of symptoms endorsed (i.e., total severity score of all items rated divided by the number of symptoms rated) on the SERS. To test the first hypothesis that patients would experience higher levels of side effects during LD and MD weeks relative to placebo, paired t-tests were used to compare the mean difference in number and severity of side effects endorsed across the three study weeks. To address baseline “side effects” hypotheses, paired t-tests were used for the patient group to compare baseline side effects to placebo, LD and MD weeks and nonparametric Mann-Whitney tests were used to compare baseline ratings between patients and siblings, given sibling ratings were not normally distributed. To evaluate the last hypothesis, linear mixed models were used to explore demographic and clinical predictors of the mean number of side effects endorsed by LD and MD compared to placebo. Data analyses were performed using SAS software (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics

Between January 2000 and January 2007, 208 patients met criteria for study participation and 138 (66%) agreed to take part in the two-day in-clinic trial. Of the 138 patients, 14 (10%) completed the in-clinic trial, but did not continue to the three-week home cross-over trial, either due to a serious adverse side effect ($n = 2$) or refusal of further participation ($n = 12$). One hundred and three SJCRH patients completed baseline screening and at least two full weeks of the home cross-over trial; only these individuals are included in data analyses (patients from other sites were not included due to missing clinical values of interest). Forty-nine healthy siblings served as a comparison group. Demographic and clinical characteristics are shown in Table 1. There were no significant gender or race differences between patients and siblings. As shown in Table 2, seven patients only completed placebo and LD weeks due to intolerability (SERS score ≥ 7) during the in-clinic trial, which resulted in *a priori* omission of MD week. Six patients were unable to tolerate MPH during the home-crossover trial and discontinued one of the medication weeks early due to side effects.

Frequency and Severity of Side Effects by MPH Dose (LD, MD and Placebo)

With respect to the first hypothesis, there was a significantly higher number and severity of symptoms endorsed on the SERS when patients were taking MD compared to placebo or LD ($ps < .001$). In contrast, there was not a significant difference between either the number or severity of symptoms endorsed on the SERS when patients were taking LD compared to placebo ($p = .143$ and $p = .635$, respectively). See Figure 1.

Frequency and Severity of Side Effects at Pre-Medication Baseline

Regarding the second hypothesis, the number of side effects endorsed on the SERS was significantly lower during all three home-cross over weeks (placebo, LD, MD) when compared to baseline symptom scores ($ps < .001$). The severity of side effects, compared to baseline screening, was significantly lower during the placebo and LD home-cross over weeks ($p < .001$ and $p = .003$, respectively), but not MD week ($p = .925$). When compared to the sibling group, both the number and severity of symptoms endorsed at baseline were significantly higher for patients than siblings ($p < .001$ and $p = .004$, respectively), consistent with our third hypothesis. See Figures 2 and 3.

Demographic and Clinical Predictors of Side Effects

Core Model Accounting for Baseline Symptoms—Given high baseline side effect ratings, the effect of baseline symptoms on mean number and severity of side effects during home-crossover was investigated using the following linear mixed model, where the response was the mean number or severity of symptoms endorsed and treatment was placebo, LD or MD taken sequentially by patient:

$$\text{Response} = \text{intercept} + \text{baseline} + \text{treatment} + \text{baseline} \times \text{treatment}$$

There was a significant interaction between baseline symptoms reported and mean number of side effects endorsed both at MD (Estimate = 0.27, $SE = 0.08$, $p = 0.0008$), where higher baseline symptom scores were significantly associated with higher side effects endorsed at MD relative to placebo, and at LD (Estimate = 0.16, $SE = 0.08$, $p = 0.03$), where higher baseline symptom scores were significantly associated with higher side effects endorsed at LD relative to placebo. There were no significant interactions between baseline symptoms and mean severity of side effects endorsed at MD or LD.

Model Including Predictors—To address the fourth hypothesis regarding predictors of side effects endorsed during the home cross-over trial, the following linear mixed model was used:

$$\text{Response} = \text{intercept} + \text{baseline} + \text{covariate} + \text{treatment} + \text{interactions}$$

Covariates entered in the model included all variables listed in Table 1 except for liver and kidney function given group means were within the average range on these variables with little variability, suggestive of infrequent pathology. When models were fitted, all interactions were examined individually and interactions with $p > .05$ were excluded from the model.

Analyses revealed that gender was significantly associated with the number of side effects endorsed, with parents of females endorsing more side effects than parents of males across all dose levels (Table 3). There was a significant interaction between estimated IQ at screening and medication dose, where a lower IQ at screening was significantly associated with more side effects endorsed at LD relative to placebo (Table 3). No other significant main effects for

covariates of interest or covariate by dose interactions were identified for number of symptoms endorsed. There were no significant predictors of mean severity of symptoms endorsed.

DISCUSSION

Study findings were generally consistent with our hypotheses. Parents rated children as experiencing significantly more frequent and severe side effects during the home cross-over trial when taking a MD relative to both placebo and LD. That said, the number of side effects endorsed during all three weeks of the home cross-over trial was lower than during baseline screening of side effects, when not prescribed any stimulant medication. Further, the severity of side effects at baseline was greater than LD but not MD. This seemingly paradoxical finding is consistent with the ADHD literature.^{12–13, 15–17} It is typically posited that some “side effects” on rating scales actually represent attention problems, which improve with stimulant medication, rather than adverse medication effects.^{13, 15, 16–17} As support for this position, patients in the current study were rated as displaying significantly more frequent and severe baseline symptoms than a healthy comparison group, in keeping with greater attention problems. Data analyses did not support the hypothesis that a BT diagnosis and higher treatment intensity would predict higher levels of side effects. Female gender and lower IQ emerged from data analyses as the only risk factors for increased side effects.

As a group, childhood cancer survivors tolerated MPH well. The frequency and severity of side effects was similar to or less than those reported on the SERS for children diagnosed with ADHD^{16–17}. As previously observed by Mulhern and colleagues,⁷ current findings revealed a subgroup of cancer survivors with decreased MPH tolerance who experience significant, and sometimes atypical, adverse side effects. A disproportionate number of cancer survivors who discontinued MPH secondary to side effects were treated for a BT. While the rate of early termination due to side effects for ALL survivors paralleled that seen in the ADHD literature^{12, 16}, the rate among BT survivors was three times higher (18.52% versus 6.12%). This finding was also observed in an open label trial conducted by De Long and colleagues.¹⁸ Among those patients completing at least two weeks of the home-crossover trial, female gender and lower IQ were risk factors for higher rates of side effects. Female gender is also a consistent risk factor for cognitive late effects in childhood cancer survivors.² The shared trait among patients identified with risk indicators of BT diagnosis, female gender and lower IQ may be greater treatment related neurological impairment that contributes to increased vulnerability to medication toxicity. It is important to note that MPH is one of the oldest and strongest stimulant medications. For children with reduced MPH tolerance, there may be alternative medication options such as atomoxetine that has demonstrated efficacy in the ADHD population^{21–23} or nonpharmaceutical cognitive remediation programs for which there is emerging support in the childhood oncology literature.²⁴

The seemingly paradoxical finding of increased side effects at baseline should be considered in relation to contextual factors that may have created a response bias. At baseline, parents completed the SERS along with other questionnaires assessing attention problems in the context of gaining admittance to an MPH study. This may have led to higher reporting of symptoms at baseline. In contrast, during the three week home-crossover, the SERS was used overtly to monitor side effects during the medication trial. Parents used the SERS to actively compare the level of symptoms from one week to the next. These findings highlight the need for baseline ratings in monitoring clinical side effects and designing clinical trials. Baseline ratings can help disentangle behaviors associated with attention problems from active treatment side effects. However, baseline ratings should not be used in lieu of a placebo control as side effects may be underestimated based on baseline alone and bias may be introduced at baseline.

The current findings should be considered in light of study limitations. The SERS is a rationally derived measure designed to assess common stimulant medication side effects. While it is the most frequently used measure for this purpose in the ADHD literature,¹³ there is a need for an empirically derived measure with demonstrated specificity for medication side effects. Even though a week long trial is generally considered adequate for monitoring medication side effects, we are in the process of gathering side effects data from a year long trial and investigating the effect of MPH on growth in cancer survivors. The current study only included indirect measures of neurological impairment (e.g., cancer diagnosis, intensity of CNS-directed therapy and hydrocephalus); future studies of MPH side effects in this population would profit from inclusion of neuroimaging findings as a more direct measure of neurological integrity.

CONCLUSION

It is imperative that clinicians and researchers monitor not only efficacy of stimulant medication but also safety in vulnerable populations, including the use of objective measures. Baseline measures are necessary to tease apart pre-existing attention problems from medication side effects.^{15, 16} Current findings suggest MPH is generally well tolerated by childhood cancer survivors; however, there are subgroups at increased risk for adverse reactions with BT diagnosis, female gender and lower IQ predictive of more frequent side effects. Those groups at increased risk need to be closely monitored by prescribing clinicians. It may also be that lower doses of MPH medication are advisable in the higher risk cancer survivors given previous findings that failed to reveal a behavioral advantage for a MD MPH over LD MPH.⁷ Given the association of side effects with discontinuing stimulant medications,^{17, 19} educating parents about the similarity among some attention symptoms and medication side effects may increase compliance.

Acknowledgments

Acknowledgements of research support: This work was supported, in part, by the Cancer Center Support (CORE) Grant P30 CA21765, R01CA078957 (awarded to Ray Mulhern, PhD), U01 CA81445 from the National Cancer Institute, and by the American Lebanese Syrian Associated Charities (ALSAC).

We thank Emily Baum, BS, Paul Chapman, MA, Melissa Jones, MA, Sue Helton, EdS, Camelia Pettis, BS, Ashley Smith, EdS, Traci Skinner, MA, Martha McCool, MS, Jason Ashford, MS, Robbin Christensen, DPh and Rhonda Simmons for their assistance in conducting this study. We thank the patients and their families who volunteered their time to participate.

Abbreviations

ADHD	attention deficit hyperactivity disorder
ALL	acute lymphoblastic leukemia
BT	brain tumors
MPH	methylphenidate
LD	low dose
MD	moderate dose

SERS

Barkley Side Effects Rating Scale

BMI

body mass index

VP

ventriculoperitoneal

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Figure 1. Side Effects- Home Cross-Over Weeks

Graphs represent the results of paired t-tests and bars depict a difference score. MD, Moderate Dose (.60 mg/kg); LD, Low Dose (.30 mg/kg); P, Placebo. * $p < .001$. The SERS is comprised of 17 symptoms rated on a scale from 0 (absent) to 9 (severe).

Figure 2. Home-Crossover Relative to Baseline “Side Effects”

Graphs represent the results of paired t-tests and bars depict a difference score. MD, Moderate Dose (.60 mg/kg); LD, Low Dose (.30 mg/kg); P, Placebo. * $p < .01$; ** $p < .001$. The SERS is comprised of 17 symptoms rated on a scale from 0 (absent) to 9 (severe).

Figure 3. “Side Effects”: Patients versus Siblings

Graphs represent the results of Mann-Whitney Tests. $*p < .01$; $**p < .001$. The SERS is comprised of 17 symptoms rated on a scale from 0 (absent) to 9 (severe).

Table 1Demographic and Clinical Characteristics (Patients $N = 103$; Siblings $N = 49$)

	Patient Group	Sibling Group	p^I
	n (%)	n (%)	
Gender			
Male	60 (58.25)	22 (44.90)	0.12
Female	43 (41.75)	27 (55.10)	
Ethnicity			
Caucasian	89 (86.41)	42 (85.72)	0.40
African American	12 (11.65)	4 (8.16)	
Other	2 (1.94)	3 (6.12)	
Patient Group ($n = 103$)	n (%)		
Diagnosis			
Brain Tumor	54 (52.43)		
ALL	49 (47.57)		
CNS Treatment Intensity			
Chemotherapy only	37 (35.92)		
≤ 24 Gy CRT $\pm$ chemotherapy	13 (12.62)		
> 24 Gy CRT $\pm$ chemotherapy	53 (51.46)		
VP Shunt to manage hydrocephalus			
No	81 (78.64)		
Yes	22 (21.36)		
	Mean $\pm$ SE (Range)		
Age at cancer diagnosis (years)	4.99 $\pm$ 0.28 (0.50 – 14.21)		
Age at MPH trial participation (years)	11.57 $\pm$ 0.30 (6.67 – 18.30)		
Length of cancer treatment (years)	1.67 $\pm$ 0.15 (0.01 – 7.82)		
Estimated baseline IQ (standard score)	87.30 $\pm$ 1.53 (52.00 – 118.00)		
BMI at MPH trial participation	21.71 $\pm$ 0.61 (14.09 – 44.18)		
Kidney function (creatinine)	0.61 $\pm$ 0.01 (0.30 – 1.00)		
Liver function (albumin)	4.24 $\pm$ 0.03 (3.30 – 5.00)		

^I Chi-square Test for gender and Fisher's Exact Test for ethnicity. Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; CRT, cranial radiation therapy; VP, ventriculoperitoneal; MPH, methylphenidate; BMI, body mass index

Table 2

Summary of Patients Missing One Week of the Home-Crossover Trial

Age at Trial Participation (years)	Gender	Cancer Diagnosis	Intolerable Dose Level	Reason
6.7	F	BT	MD (discontinued)	Irritable, labile mood
7.9	F	BT	MD (discontinued)	Irritable, crying
12.3	M	BT	MD (discontinued)	Hyperkinetic, insomnia
15.8	M	BT	MD (discontinued)	Labile mood, crying
16.8	F	BT	MD (discontinued)	Agitation, tachycardia
14.4	F	ALL	LD (discontinued)	Chest pains
7.2	M	BT	MD (omitted)*	Labile mood, confusion
7.3	M	BT	MD (omitted)	Tics, incessant talking
7.8	F	ALL	MD (omitted)	Hyper vigilant, excitable
9.2	F	BT	MD (omitted)	Facial tics, incessant talking
9.2	M	BT	MD (omitted)	High BP, dizziness
10.2	M	BT	MD (omitted)	Nausea, lack of energy
11.9	F	ALL	MD (omitted)	Nausea, vomiting

Abbreviations: BT, brain tumor; ALL, acute lymphoblastic leukemia; M, male; F, female; P, placebo; LD, low dose (0.30 mg/kg bid, maximum dose 10 mg); MD, moderate dose (0.60 mg/kg bid, maximum dose 20mg); BP, blood pressure

* The seven patients with an omitted MD week experienced significant side effects during the initial challenge of MPH (SERS score ≥ 7); these side effects during the two-day in-clinic trial resulted in *a priori* omission of MD week.

Table 3

Analyses of Demographic and Clinical Predictors of SERS Number of Side Effects Endorsed

Effect	Condition	Estimate	SE	P
Intercept		1.56	0.58	0.008 [*]
Baseline Symptoms		0.10	0.07	0.177
Gender	Female	0.96	0.49	0.049 ^{*1}
	Male	0		
Treatment	LD	-0.57	0.59	0.335
	MD	-0.23	0.62	0.712
	P	0		
Baseline * Treatment	LD	0.16	0.08	0.033 ^{*2}
	MD	0.27	0.08	0.001 ^{*2}
	P	0		
Intercept		1.61	1.84	0.381
Baseline Symptoms		0.097	0.07	0.174
Estimated IQ		0.00	0.02	0.841
Treatment	LD	4.16	1.94	0.033 ^{*2}
	MD	-0.65	2.02	0.748
	P	0		
Baseline * Treatment	LD	0.15	0.07	0.044 ^{*2}
	MD	0.27	0.08	0.000 ^{*2}
	P	0		
Estimated IQ * Treatment	LD	-0.05	0.02	0.012 ^{*2}
	MD	0.00	0.02	0.838
	P	0		

* Statistical significance as indicated by $p < .05$.

¹ p-value for difference between gender, where male is set to 0.

² p-values for difference from placebo across other variables, where placebo is set to 0. Abbreviations: P, placebo; LD, low dose (0.30 mg/kg bid, maximum dose 10 mg); MD, moderate dose (0.60 mg/kg bid, maximum dose 20mg).