Attention-Deficit/Hyperactivity Disorder Medication Treatment Impact on Response to Growth Hormone Therapy: Results from the ANSWER Program, a Non-Interventional Study

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Objective To examine whether attention-deficit/hyperactivity disorder (ADHD) stimulant medication modified the linear growth response to growth hormone (GH) treatment in children enrolled in the American Norditropin Studies: Web-Enabled Research Program.

Study design Short, GH treatment-naive children with or without GH deficiency (GHD) received GH therapy. A subset also received ADHD stimulant medication (n = 1190), and others did not (n = 7230). Linear mixed models (adjusted means) examined height SDS (HSDS) and body mass index (BMI) SDS from baseline through year 4. Analyses were repeated with ADHD groups matched for baseline age, height, weight, BMI, and sex. Groups with and without GHD were compared between ADHD groups.

Results Adjusted change in HSDS for the group receiving ADHD stimulant medication was slightly lower than that for patients not receiving stimulant medication at years 1 to 4 ($P < .05$). However, adjusted change in HSDS was similar between children receiving and not receiving ADHD stimulant medication when matched for baseline measurements. At year 4, 86.7% of patients receiving ADHD stimulant medication, 86.8% of total patients not receiving ADHD stimulant medication, and 84.6% of matched group patients not receiving ADHD stimulant medication achieved HSDS >−2. Year 4 adjusted change in BMI SDS was greater in the patients receiving ADHD stimulant medication compared with both groups not receiving ADHD stimulant medication ($P < .05$). Patients with GHD showed comparable differences in adjusted change in BMI SDS among the ADHD groups at year 4, whereas patients without GHD showed no significant differences.

Conclusions ADHD medication did not affect the linear growth response of children treated with GH when those receiving or not receiving ADHD stimulant medication were matched for baseline measurements. Underlying reasons for the observed greater increase in BMI in patients with GHD concomitantly treated with ADHD medication remain to be elucidated. *(J Pediatr 2015;167:1389-96)*.

Trial registration ClinicalTrials.gov: NCT01009905.

Recombinant human growth hormone (GH) treatment is approved by the US Food and Drug Administration for children with linear growth failure or short stature due to GH deficiency (GHD), idiopathic short stature (ISS), Turner syndrome, Noonan syndrome, Prader-Willi syndrome, short stature homeobox-containing gene deficiency, chronic renal disease, and children born small for gestational age (SGA) with no catch-up growth by 2 to 4 years of age.[1,2] The goal of GH treatment across pediatric indications is to improve linear growth in childhood and to achieve an adult height within the normal range.[3,4]

To achieve optimal height outcomes, it is important to consider potential comorbid conditions that may influence growth and GH treatment response. Attention-deficit/hyperactivity disorder (ADHD) may be an important growth-influencing comorbidity during GH treatment because of the frequent use of psychostimulants as first-line psychopharmacologic therapy.[5,6] Some children taking ADHD stimulant medications experience a loss of appetite, weight loss, and a decrease in height and weight increments.[7-9] A review of studies examining growth in children with ADHD who receive stimulant medication suggested that in children with short stature, a minor medication effect on growth velocity could be clinically important.[10] Two previous studies using data from the National Cooperative Growth

ADHD	Attention-deficit/hyperactivity disorder	ISS	Idiopathic short stature
ANSWER	American Norditropin Studies: Web-Enabled Research	KIGS	Pfizer International Growth Study
BMI	Body mass index	NCGS	National Cooperative Growth Study
GH	Growth hormone	SGA	Small for gestational age
GHD	GH deficiency	ΔBMI SDS	Change in BMI SDS
HSDS	Height SDS	ΔHSDS	Change in height SDS
IGF-I	Insulin-like growth factor-I		

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Study (NCGS) database showed that children taking ADHD stimulant medications do not have clinically significant differences in growth compared with children not taking stimulant medications during GH treatment.[6,11] A study from the Pfizer International Growth Study (KIGS) registry found 1-year GH therapy growth response in stimulant-treated children with ADHD and GHD was significantly less than the expected growth in children with GHD based on previously developed growth prediction statistical models.[12,13] In the KIGS study, no significant differences between children with stimulant-treated ADHD or without ADHD were seen in children with ISS, SGA, or Turner syndrome using growth prediction models. Additionally, a study of short SGA children treated with GH with or without methylphenidate treatment for ADHD showed no negative effect of stimulant treatment on adult height.[14] Thus, the potential effects of ADHD stimulant medications on linear growth and weight responses among pediatric GH treatment indications remain to be clarified. The current study examines the effect of ADHD medications on change in height SDS (ΔHSDS) and change in body mass index (BMI) SDS (ΔBMI SDS) over a 4-year period of GH therapy in pediatric patients enrolled in the American Norditropin Studies: Web-Enabled Research (ANSWER) Program.

Methods

Data for this analysis were obtained from the ANSWER Program, a non-interventional study (ClinicalTrials.gov: NCT01009905) collecting long-term effectiveness and safety information from patients treated with Norditropin (somatropin [rDNA origin] injection, Novo Nordisk A/S, Bagsvaerd, Denmark)[15] in the US. The ANSWER Program (utilizing the research Web-based platform, NovoNet) has collected effectiveness and safety information on >13 000 pediatric patients since 2002.[16] Participation within the ANSWER Program is at the discretion of the participating physicians and includes pediatric patients with diagnostic conditions of short stature or growth failure treated with GH. Participating physician investigators entered patient histories and physical examination data using the Web-based data entry tool. The current study analyzed only GH treatment-naive patients age ≤18 years with the diagnosis of GHD (as determined by the participating physician, including isolated/idiopathic or multiple pituitary hormone deficiency), or with non-GHD short stature, including Turner syndrome, Noonan syndrome, SGA, ISS, Prader-Willi syndrome, and other short-stature conditions (eg, chronic renal disease, short stature homeobox-containing gene deficiency). Enrollment in this patient registry is solely at the discretion of the participating physicians and for patients in whom Norditropin is prescribed for treatment of appropriate conditions of growth failure and short stature both within and outside the Norditropin label. All participants provided written informed consent prior to entry into the study and were free to discontinue treatment at any time. The collected data were anonymous. The study protocol was approved by an institutional review board and carried out in accordance with Good Pharmacoepidemiologic Practice guidelines.

Patients were categorized as those receiving ADHD medication (n = 1190), including dextroamphetamine and amphetamine, amphetamine, pemoline, methylphenidate, or other; and those not receiving ADHD medication (n = 7230). Data analyses compared patients receiving and not receiving stimulant medication. Patients who did not have the data entry field completed, indicating treatment with or without ADHD medication (n = 969), were excluded from the comparisons. Clinical data recorded at baseline included age, sex, height, weight, BMI SDS, height SDS (HSDS), insulin-like growth factor-I (IGF-I) SDS, and bone age. HSDS and BMI SDS were calculated according to the standard formulas provided by the Centers for Disease Control and Prevention.[17] All IGF-I values were measured locally and entered into the database. Transformation of IGF-I data into IGF-I SDS was then made based on the age- and sex-related normative reference values of Brabant et al.[18] Clinical data collected at 4 months and years 1 through 4 of GH treatment included HSDS, BMI SDS, and GH dose.

Statistical Analyses

Data were collected at 4 months within a ±1-month window and at 1 through 4 years within a ±3-month window. To eliminate potential data errors, patients with data outliers were excluded from the analysis when key variables (age, height, weight, etc.) were missing or deemed implausible. Demographic characteristics and descriptive data are presented as mean ± SD or percentages. Children younger than 2 years of age were excluded from the BMI analyses because of a lack of appropriate reference data for this age group. Comparisons between the above groups of ΔHSDS and ΔBMI SDS from baseline to 4 months and years 1 through 4 were summarized using arithmetic means (unadjusted ΔHSDS and ΔBMI SDS) and least squares means (adjusted ΔHSDS and ΔBMI SDS). To compare ΔHSDS and ΔBMI SDS between the groups at each time point, ANCOVA with ADHD medication use as the fixed effect and baseline HSDS value or BMI value as the covariate was performed. For the analysis of ΔHSDS, the ANCOVA model also included age and sex as covariates. Across the study time points, the ANCOVA models used different subcohorts of the subject population because of varied missing data at each time point. Fisher exact test was used to compare the proportion of patients achieving HSDS >−2 (ie, within normal range) at year 4.

Because of differences in baseline age and associated measurements between the patients receiving or not receiving ADHD stimulant medication, additional analyses were conducted with a subgroup of patients not receiving ADHD stimulant medication who were matched to the baseline age, height, weight, BMI, and sex of the patients receiving ADHD stimulant medication. Results are first presented as comparison between the total group receiving ADHD stimulant medication and total group not receiving ADHD medication. Results are then presented comparing the total group receiving ADHD stimulant medication with the matched