Methylphenidate in children with monogenic obesity due to LEPR or MC4R deficiency improves feeling of satiety and reduces BMI-SDS—A case series

Stephanie Brandt1 | Julia von Schnurbein1 | Belinda Lennerz1,2 | Katja Kohlsdorf1 | Heike Vollbach1,3 | Christian Denzer1 | Harald Bode4 | Johannes Hebebrand5 | Martin Wabitsch1

1Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany
2Division of Endocrinology and New Balance Foundation Obesity Prevention Center, Boston Children’s Hospital and Harvard Medical School, Harvard University, Boston, Boston, Massachusetts
3Pediatric Endocrinology and Diabetology Division, Children’s Hospital, University of Bonn, Bonn, Germany
4Pediatric Endocrinology and Neurology, University Children’s Hospital, Ulm, Germany
5Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Universitätsklinikum Essen (AöR), Essen, Germany

Correspondence
Prof. Dr. med. Martin Wabitsch, Center for Rare Endocrine Diseases, Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm 89075, Germany.
Email: martin.wabitsch@uniklinik-ulm.de

Funding Information
Hertha-Nathorff-Programm, Grant/Award Number: LSSH1000.07; KSKI 002.1

Summary
Background: The clinical phenotype of patients with monogenic obesity due to mutations in the leptin receptor (LEPR) or melanocortin 4 receptor (MC4R) gene is characterized by impaired satiety and hyperphagia, leading to extreme, sometimes life-threatening weight gain.
Subjects/methods: In a case series, we analysed the effect of an off-label methylphenidate (MPH) use for 1 year as an individual treatment approach on eating behaviour (Child Eating Behaviour Questionnaire [CEBQ]), appetite (visual analogue scales) and body mass index (BMI) trajectories in five patients with severe obesity due to mutations in the LEPR (n = 3) or MC4R (n = 2) gene.
Results: After 1 year use of MPH (20 mg/day divided in two to three doses), BMI (Δ BMI0–T1: x: −0.7 ± 0.9 kg/m²), BMI standard deviation score (SDS) (Δ BMI-SDS0–T1: x: −0.32 ± 0.20), and %BMIP95 (Δ %BMIP950–T1: x: −6.6 ± 7.8%) decreased. BMI-SDS velocity decreased from +0.17 ± 0.22 to −0.30 ± 0.20. Appetite and CEBQ subscale scores for “food responsiveness” and “enjoyment of food” decreased. We observed adverse effects with increase in self-reported frequency of disordered sleep, nervousness, hyperactivity, and tics.
Conclusions: The observed decrease in BMI trajectories with MPH use for one year is clinically meaningful in this group of patients, since the natural course would have been associated with a pronounced increase in BMI, leading to comorbidities and complications over time.

KEYWORDS
central nervous system, MC4R mutation, methylphenidate, monogenic obesity, LEPR mutation

1 | INTRODUCTION

Monogenic obesity is caused by mutations in the hypothalamic leptin-melanocortin pathway and accounts for 1% to 5% of cases of severe childhood obesity.1 The most common form is caused by heterozygous mutations in the melanocortin 4 receptor gene (MC4R).2,3 Other causes are, eg, biallelic mutations in the leptin gene (LEP), leptin receptor gene (LEPR), or proopiomelanocortin gene (POMC)4–7.
The adipocyte hormone leptin regulates body fat mass and energy homeostasis by modulating energy intake and expenditure, autonomic nervous system tone, and neuroendocrine functions. The hypothalamic leptin-melanocortin pathway plays a key role in mediating these effects. Leptin’s interaction with its hypothalamic receptor activates POMC/cocaine- and amphetamine-regulated transcript (CART) neurons and deactivates agouti-related protein (AgRP)/neuropeptide Y (NPY) neurons in the arcuate nucleus. It thereby inhibits the production of NPY and AgRP and induces the production of CART and POMC. POMC is a polypeptide that undergoes tissue-specific posttranslational processing. The products of which include the melanocortin peptides α-, β-, and γ-melanocyte-stimulating hormone (MSH). α-MSH activates, while AgPR deactivates MC4R in second-order neurons in the paraventricular nucleus. However, β-MSH is also capable of activating MC4R. MC4R activation in these neurons induces anorexigenic signals to affect food intake and energy expenditure through interaction with higher cortical centres, including dopaminergic neurons in the mesolimbic system.

Patients with disruptions of these pathways demonstrate impaired satiety, hyperphagia, and food-seeking behaviours leading to early onset severe obesity. Lifestyle interventions are largely unsuccessful. Children with pathogenic LEPR mutations show a tremendous increase in body mass index (BMI) during the first 2 years of life. Compared with them, patients with MC4R mutations have later onset obesity with significantly lower BMI values. Unlike leptin deficiency where leptin replacement has been proven successful, LEPR or MC4R deficiency have no causal treatment. Hence, other treatment options are needed to prevent the rapid progression of obesity and associated complications.

MPH is frequently used in the treatment of children with attention deficit hyperactivity disorder (ADHD) because it reduces hyperactivity and enhances attention. Reduced appetite and weight loss are among the most common side effects and are likely mediated by leptin’s interaction with its hypothalamic receptor. MPH use was started as a single dose of 5 or 10 mg/day and titrated to effect up to a maximum dose of 20 mg/day divided in two to three doses. Follow-up was recommended at 3-month intervals to assess eating behaviour, appetite, height and weight, and adverse events as outlined below. Before starting MPH treatment, patients and parents were informed comprehensively about the off-label use and potential benefits and risks of MPH by trained paediatricians. Written informed consent was given by the parents. Baseline evaluation for contraindications for MPH (seizure disorders, depression, mood disorders, cardiovascular disease, hypertension, and arrhythmia) included a neurologic examination by a paediatric neurologist, a psychological evaluation by a clinical psychologist, and an in-depth cardiologic evaluation by a paediatric cardiologist including echocardiogram, electrocardiogram, and blood pressure measurements. MPH use was started as a single dose of 5 or 10 mg/day and titrated to effect up to a maximum dose of 20 mg/day divided in two to three doses. Follow-up was recommended at 3-month intervals to assess eating behaviour, appetite, height and weight, and adverse events as outlined in the following sections. Baseline (T0) and 1-year follow-up (T1) data are presented.

2 SUBJECTS AND METHODS

2.1 Study population

In a retrospective case series, we report data of n = 5 patients who presented to our outpatient clinic (2005-2013) with severe obesity early in childhood due to pathogenic mutations in the LEPR (n = 3) or MC4R (n = 2) gene. Clinical characteristics of three of the patients have been previously published.

After unsuccessful conventional treatment approaches including dietary and behavioural lifestyle interventions, the families of these patients agreed to off-label methylphenidate (MPH) use as an individual treatment using to control weight gain. An off-label individual treatment describes the application of an approved drug but in an indication for which it is not approved. Patients receive an off-label treatment with MPH in an individual case, which the physician decides on his own initiative and with the patient’s consent within the framework of freedom of therapy (in accordance with item 32 of the Declaration of Helsinki; version 2000). Patients were treated and monitored according to a standardized clinical protocol as outlined below. Before starting MPH treatment, patients and parents were informed comprehensively about the off-label use and potential benefits and risks of MPH by trained paediatricians. Written informed consent was given by the parents. Baseline evaluation for contraindications for MPH (seizure disorders, depression, mood disorders, cardiovascular disease, hypertension, and arrhythmia) included a neurologic examination by a paediatric neurologist, a psychological evaluation by a clinical psychologist, and an in-depth cardiologic evaluation by a paediatric cardiologist including echocardiogram, electrocardiogram, and blood pressure measurements. MPH use was started as a single dose of 5 or 10 mg/day and titrated to effect up to a maximum dose of 20 mg/day divided in two to three doses. Follow-up was recommended at 3-month intervals to assess eating behaviour, appetite, height and weight, and adverse events as outlined in the following sections. Baseline (T0) and 1-year follow-up (T1) data are presented.

2.2 Child Eating Behaviour Questionnaires

A German translation of the Child Eating Behaviour Questionnaires (CEBQ) was completed by the parents at initiation of MPH use (T0) and at the 1-year follow-up (T1). This questionnaire is routinely used in our outpatient clinic to assess eating behaviour in patients with severe obesity. The CEBQ consists of 35 questions that are categorized in eight subscales: food responsiveness, enjoyment of food, slowness in eating, food fussiness, satiety responsiveness, emotional overeating, emotional undereating, and desire to drink. Answers are recorded on a 5-point Likert scale where specific eating behaviours are quantified as never, rarely, sometimes, often, and always. Questions were scored as per Wardle et al. Scores for each subscale were calculated as the average score of the individual questions. Subscales were then grouped into two categories: (a) food approach, which summarizes the categories food responsiveness, enjoyment of food, emotional overeating, and desire to drink and (b) food avoidance, which comprises slowness in eating, food fussiness, satiety responsiveness, and emotional undereating.

2.3 Appetite and adverse effects

Visual analogue scales (VAS) with anchors 0 = never and 10 = always are routinely used in our outpatient clinic to get information about
appetite in patients with severe obesity and were also used to assess the presence of disordered sleep, nervousness, hyperactivity, impulsivity, tics, aggression, and headaches. In addition, treating physician-documented adverse events using standardized questions covering cardiovascular (palpitations, tachycardia), central nervous system (CNS) (aggressiveness, dysphoria, tics, headache, restlessness, insomnia), dermatologic (alopecia, urticaria), gastrointestinal (constipation, diarrhoea), neuromuscular (dyskinesia, tremor), and ophthalmic (blurry vision) reactions at each visit. Reported side effects of MPH intake regarding laboratory parameters are hypertension (frequent), elevated liver enzyme levels (frequent), anaemia (very rare), and leukopenia (very rare). Systolic and diastolic blood pressure (mmHg) as well as concentrations of liver enzymes (aspartate aminotransferase [AST, U/L], alanine aminotransferase [ALT, U/L], gamma-glutamyl transferase [GGT, U/L]), concentrations of leukocytes (Giga/L), erythrocytes (Tera/L), thrombocytes (Giga/L), and the haemoglobin (g/dL) value were measured routinely during the outpatient visit. Blood pressure (systolic and diastolic) was measured with a calibrated blood pressure monitor (DINAMAP, Critikon, Germany, North Rhine-Westphalia) while the child lies on his/her back (after staying in a lying position for at least 5 minutes).

2.4 | Anthropometric data

All children in Germany have 10 well-child examinations between birth and the age of 5 years to assess psycho-motor development and provide health surveillance. Results (including measured weight and height) are recorded in health booklets. Additional height and weight measurements were available from medical records.

At all visits to our outpatient clinic, body weight was measured to the nearest 0.1 kg on a calibrated balance beam scale (Seca, Hamburg, Germany), and body height was measured to the nearest 0.1 cm (Stadiometer, Busse Design, Ulm, Germany).

BMI was calculated by dividing weight (in kilograms) by the square of height (in meters). BMI was classified for children using the 90th/97th age- and sex-specific percentiles of the German reference data as cut-off point for overweight/obesity. BMI-SDS was calculated using the least mean squares method based on German references. In addition, the degree of obesity was expressed as percentage of the 95th percentile (%BMIP95) of the Center of Disease Control and Prevention (CDC) BMI percentiles (2-20 years), as recommended recently in the Endocrine Society Clinical Practice Guideline for paediatric obesity.

Because of the observational nature of this case series, follow-up intervals were not consistent. Hence, not all patients had follow-up information at exactly 12 months (intervals between 9 and 15 months). To adjust for different follow-up intervals, we calculated the extrapolated annualized BMI-SDS velocity by dividing the change in BMI-SDS by the observation interval in months and then multiplying by 12 months. This is analogous to the routinely performed calculation of height or weight velocity. A retrospective chart review was conducted to establish BMI-SDS velocity prior to initiation on MPH use. To assess the effect of MPH on longitudinal growth, the annualized growth velocity defined as change in body height per year (cm per year) as well as change in height SDS between T0 and T1 was calculated.

2.5 | Continuation of off-label individual MPH treatment after T1

Duration of off-label individual treatment with MPH varies between the five patients from 1.2 up to 4 years. Since all patients received MPH for 1 year, the time point “12 months after the start of off-label MPH treatment (T1)” was determined as the primary endpoint to investigate the effects of an off-label MPH treatment on eating behaviour, appetite, and BMI trajectories in children with severe obesity due to mutations in the LEPR or MC4R gene. In patient A, the off-label MPH treatment was stopped after 2 years as the patient was included in a clinical study. In patient B, the parents stopped the off-label treatment with MPH after 1.2 years, because the parents did not want to give their child any medication and wanted to control the BMI by strictly controlling the lifestyle. Two other patients (patients C and D) are still on individual off-label MPH treatment. Patient E took MPH very irregularly after the first year of treatment and interrupted it several times on the initiative of the parents. The parents have reported serious problems in the family that led the parents forgetting to give their child MPH. Furthermore, parents did not come to the outpatient clinic for appointments and for this reason, they received no prescription for MPH.

2.6 | Statistics

Descriptive data analyses and BMI trajectories were computed using the Graph Pad Prism 7 (Graph Pad Software Inc, San Diego, CA). Data are presented as single data per patient and/or as mean and standard deviation (SD) for the group. Student t test was used for statistical comparisons. A P value (two-sided) of less than 0.05 was considered significant.

3 | RESULTS

3.1 | Patient characteristics

Four of five patients (three females and two males) were born full-term, and all patients were born appropriate for gestational age (data not shown). All patients had BMI-SDS values greater than 1 at 1 year of age (range BMI-SDS 1 year: 1.2-6.19) and BMI-SDS values greater than 3 at 2 years of age (range BMI-SDS 2 years: 3.32-6.02). Age at initiation of off-label MPH treatment ranged between 2.8 and 14.9 years (Table 1a).

3.2 | Eating behaviour (CEBQ)

At initiation of off-label MPH treatment, children had the highest scores in the pro-intake subscales “enjoyment of food,” “desire to drink,” and “food responsiveness” of the CEBQ. The subscale “FOOD
RESPONSIVENESS” includes statements like “my child is always asking for food” or “given the choice, my child would eat most of the time.” The subscale “enjoyment of food” includes the statements “my child loves food” or “my child looks forward for meal times” or “my child is interested in food.” After 1 year of off-label MPH treatment, scores in the subscales “food responsiveness” and “enjoyment of food” decreased significantly (Figure 1).

### 3.3 | Appetite

Patients reported high frequency of appetite at T0, with a significantly decreased frequency at T1. Mean value for appetite at the VAS was 8.3 ± 1.6 out of 10 at T0 and 3.5 ± 2.4 at T1 (P < .05) (Figure 2).

### 3.4 | Changes in BMI, BMI-SDS, and %BMIP95

Figure 3 shows that all patients showed an immediate onset of rapid weight gain with the most rapid increase during their first year of life. All patients were affected by obesity at T0, (x BMI-SDS: 4.3 ± 0.7, Table 1b). After 1 year of off-label MPH use, BMI values declined (Δ BMI; T0–T1 x: −0.7 ± 0.9 kg/m², range: 0.7 to −1.9 kg/m², P > .05) (Figure 3). Patient C had the greatest reduction in BMI of −1.9 kg/m² (Table 1b). BMI-SDS significantly decreased with off-label MPH use (Δ BMI-SDS; T0–T1 x: −0.32 ± 0.20, range: −0.03 to −0.64, P < .05). The two youngest patients (patient B and patient E) had the highest reductions in BMI-SDS. %BMIP95 decreased after 1 year of MPH use (Δ %BMIP95; T0–T1 x: −6.6 ± 7.8%, P > .05, range: +5 to −17%, P > .05), with a maximum difference of −17% in patient C (Table 1b).

### 3.5 | Change in BMI-SDS velocity

Mean BMI-SDS velocity in the year before off-label MPH use was +0.18 ± 0.30. As shown in Figure 4, BMI-SDS velocity decreased significantly on MPH and reached a negative level −0.32 ± 0.20 (range: −0.03 to −0.64, P < .05, Table 1b).

### 3.6 | Adverse effects

Most patients reported higher rates of disordered sleep (T0: x=0.9 ± 1.2; T1: x=0.1 ± 2.9; P > .05), nervousness (T0: x=1.6 ± 2.4; T1: x=3.1 ± 3.0; P > .05), hyperactivity (T0: x=0.7 ± 0.9; T1: x=2.4 ± 2.7; P > .05), and tics (T0: x=0.0 ± 0.0; T1: x=1.7 ± 3.0; P > .05) at T1 compared with T0, but this did not reach significance across the group (Figure 2). None of these side effects led to a discontinuation of MPH use. There was no meaningful change in height SDS between T0 and T1 (Δ height SDS; T0–T1 = −0.04 ± 0.22; data not shown). No additional physician-recorded adverse events were reported.

One patient already had arterial hypertension at the beginning of off-label MPH treatment. The patient was treated with Ramipril (first: 2.5 mg/day, in the course: increase to two times 2.5 mg/day). No worsening of spontaneous blood pressure measurement occurred during off-label MPH treatment over 1 year (Figure S1). The systolic blood pressure remained stable in four patients (Figure S1). One patient showed a lower systolic blood pressure at T1 than at T0. The diastolic blood pressure remained stable in four patients. In one patient, the diastolic blood pressure increased from 54 to 74 mmHg. This value is still within the normal range. We observed an increase in liver enzyme levels of AST, ALT, and GGT in one (patient B) of the five patients under off-label MPH treatment for 1 year (AST: T0 = 33 U/L, T1 = 125 U/L; ALT: T0 = 51 U/L, T1 = 212 U/L; GGT T0 = 14 U/L, T1 = 32 U/L). The liver enzyme values were above the reference range but were not in the dangerously elevated range. Since the patient benefited from the off-label MPH treatment with regard to a stabilization in BMI values, the treatment was continued under the condition of tight control of the liver enzyme levels. After stopping the off-label MPH treatment by the parents (after 1.2 years), the liver enzyme levels normalized. Anaemia or leucopenia was not observed in any of the patients receiving an individual off-label MPH treatment over 1 year (data not shown).

### 3.7 | Continuation of off-label individual MPH treatment after T1

As shown in Figure S2, in two patients, off-label MPH treatment was stopped after 1.2 and 2 years (Figure S2A,B). In those, off-label MPH treatment showed stabilization or further reduction in the BMI after

### Table 1A

Table 1A (characteristic gene mutation, sex, anthropometrics [BMI, BMI-SDS] at birth, at 1 and at 2 y, age at initiation of off-label methylphenidate treatment [T0]) in n = 5 patients with severe obesity due to mutations in the LEPR or MC4R gene

| Patient | Gene Mutation | sex | BMI at Birth, kg/m² | BMI at 1 y, kg/m² | BMI at 2 y, kg/m² | BMI-SDS at Birth | BMI-SDS at 1 y | BMI-SDS at 2 y | Age at T0, y |
|---------|---------------|-----|---------------------|------------------|------------------|----------------|----------------|----------------|-------------|
| A       | LEPR (homozygous: c.2051A>C) | ♂   | 10.1                | 28.1             | 28.9             | −1.95          | 5.89           | 4.79           | 9.8         |
| B       | LEPR (homozygous: c.453delC)  | ♂   | 11.5                | 29.0             | 36.5             | −0.91          | 6.19           | 6.02           | 2.8         |
| C       | LEPR (double homozygous: c.946C>A; c.1938G>T) | ♂   | 10.7                | 26.7             | 26.7             | −1.51          | 5.39           | 4.73           | 7.4         |
| D       | MC4R (heterozygous: c.380C>T) | ♀   | 13.2                | 18.6             | 22.7             | 0.51           | 1.20           | 3.32           | 14.9        |
| E       | MC4R (heterozygous: c.453delC) | ♀   | 13.1                | 28.2             | 28.8             | 0.43           | 4.95           | 4.49           | 3.2         |

**Abbreviations:** BMI, body mass index; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; SDS, standard deviation score.

*Patient A: BMI at 3 y; patient B: BMI at 2.8 y, patient E: BMI at 3 y.
FIGURE 1  Mean scores of the subscales "food responsiveness, emotional over-eating, enjoyment of food, desire to drink, satiety responsiveness, slowness in eating, emotional under-eating, and food fussiness" assessed by the Child Eating Behaviour Questionnaire (CEBQ) at initiation of off-label individual methylphenidate treatment (T0: circles) and after 1 y of off-label individual methylphenidate treatment (T1: triangle) in n = 5 patients with severe obesity due to mutations in the leptin receptor (LEPR) or melanocortin 4 receptor (MC4R) gene. A, Score "desire to drink"—questions: My child is always asking for a drink; If given the chance, my child would drink continuously throughout the day; If given the chance, my child would always be having a drink; B, score "food responsiveness"—questions: My child is always asking for food; If allowed to, my child would eat too much; Given the choice, my child would eat most of the time; Even if my child is full up s/he finds room to eat his/her favourites food; If given the chance, my child would always have food in his/her mouth; C, score "emotional overeating"—questions: My child eats more when worried; My child eats more when annoyed; My child eats more when anxious; My child eats more when s/he has nothing else to do; D, score "enjoyment of food"—questions: My child loves food, My child is interested in food, My child enjoys eating; E, score "food Fussiness"—questions: My child refuses new foods at first; My child enjoys tasting new foods, My child enjoys a wide variety of foods, My child is difficult to please with meals, My child is interested in tasting food s/he hasn't tasted before, My child decides that s/he doesn't like a food, even without tasting it; F, score "emotional undereating"—questions: My child eats less when angry, My child eats less when upset, My child eats less when s/he is tired. My child eats more when she is happy, My child eats less when s/he is tired, My child eats more when s/he finds room to eat his/her favourites food; If given the chance, my child would always have food in his/her mouth; C, score "emotional undereating"—questions: My child has a big appetite, My child leaves food on his/her plate at the end of a meal, My child gets full before his/her meal is finished, My child gets full up easily, My child cannot eat a meal if s/he has had a snack just before; G, score "satiety responsiveness"—questions: My child eats more when worried; My child eats more when annoyed; My child eats more when anxious; My child eats more when s/he has nothing else to do; H, score "slowness in eating"—questions: My child finishes his/her meal quickly, My child eats slowly, My child takes more than 30 minutes to finish a meal, My child eats more and more slowly during the course of a meal (score: 0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = always)

the first year of treatment. Patient B showed a slight increase in BMI after stopping MPH therapy. Patients C and D are still on off-label MPH treatment (Figure S2C,D). Patient C showed stable BMI values under off-label MPH treatment after the first year. Patient D showed initially also stable BMI values. As a result of entering professional life, the BMI increased during the further course of off-label MPH treatment. The patient succeeded in keeping the BMI stable again in the further course of the off-label MPH treatment. Patient E took MPH regularly only in the first year (Figure S2E). Thereafter, the intake was irregular, but the BMI continued to decrease under off-label MPH treatment. The parents stopped the treatment with MPH of the child at the age of 8 years. An increase in BMI can be observed immediately. To sum up, the few long-term data show that a continuation of off-label MPH treatment after the first year probably does not result in a further BMI reduction but rather in a BMI stabilization.

4 | DISCUSSION

In an observational case series, we analysed the effect of an off-label individual treatment with MPH for 1 year in five children with monogenic obesity due to mutations in LEPR or MC4R gene. We reported changes in weight trajectories as quantified by BMI, BMI-SDS, and BMI-SDS velocity, eating behaviour and appetite, as well as MPH adverse effects.

"Enjoyment of food" and "food responsiveness" (assessed by CEBQ), self-reported appetite (assessed by VAS), and mean BMI, BMI-SDS, and BMI-SDS velocity decreased in a clinically meaningful way. Self-reported frequency of disordered sleep, nervousness, hyperactivity, and tics increased in most patients but did not reach significance across the group and did not lead to discontinuation of MPH. No additional adverse events were reported by physicians.

Children with LEPR mutations are characterized by pronounced hyperphagia leading to a tremendous increase in BMI during the first 2 years of life. Although patients with MC4R mutations generally have lower BMI and a later onset of obesity, both groups display severe obesity in early childhood and have a high risk of developing comorbidities and complications. Lifestyle interventions are unsuccessful at large. Very recently, it has been reported that patients with LEPR mutations can be treated successfully with a new melanocortin receptor agonist, setmelanotide. To date setmelanotide is available only
within clinical studies and only for patients older than 6 years of age. Outside of clinical studies, there is no effective treatment available for patients with \( \text{LEPR} \) or \( \text{MC4R} \) mutation.

All children in this case series were affected by hyperphagia, excessive weight gain, and severe early onset obesity refractory to lifestyle intervention. Because hyperphagia is a cardinal feature of monogenic obesity, a plausible candidate approach might be the use of substances that impact appetite and satiety regulation. MPH has been the first choice in the pharmacological treatment of ADHD for many years, and extensive safety data are available in school-aged and younger children. Poor appetite and weight loss are among the most common side effects. We have chosen an off-label individual treatment option with off-label use of MPH to influence appetite and satiety and slow down the exaggerated weight gain in our group of patients.

We used the CEBQ to assess eating behaviour before and 1 year after starting MPH use. Two subscales of the CEBQ were significantly affected by MPH: "enjoyment of food" and "food responsiveness." We observed a strong decrease in the scores of these two subscales. The baseline score of 2.4 in the subscale "food responsiveness" was consistent with published values of 2.2 for overweight boys and 2.4 for overweight girls \( (n = 1,058 \text{ children}; 7-10 \text{ years}) \). With MPH, "food responsiveness" decreased to a score of 1.3, consistent with reported values in normal-weight children. In addition, patients had a significant reduction in self-reported appetite.

We documented a significant decrease in BMI, BMI-SDS, and BMI-SDS velocity after 1 year of MPH use in five children with monogenic obesity due to mutations in \( \text{LEPR} \) or \( \text{MC4R} \) gene. Several reports quantify the effect of MPH on anthropometric parameters in children with ADHD. Two studies reported long-term reductions in body weight of \(-1.2 \text{ kg after 21 months}\) and of \(-1.6 \text{ kg after 48 months on MPH}\). One trial describing MPH for 3 years and 3 months showed that half of the children with a BMI-SDS greater than 1.5 maintained, while the other half reduced their BMI-SDS.

MPH effects on weight and appetite are likely mediated by a combination of direct and indirect sympathomimetic effects, as well as brain reuptake inhibition of norepinephrine and dopamine.

MPH binds to and inhibits pre-synaptic norepinephrine (NET) and dopamine transporters (DAT), leading to decreased reuptake and thus increased synaptic norepinephrine and dopamine concentrations, both targets for many weight-loss drugs. Dopamine is a key transmitter in the meso-limbic system signalling food reward and craving. Evidence from animal and human studies demonstrate altered dopamine signalling in individuals with obesity compared with individuals with normal weight possibly due to rapid dopamine transport and/or reduced numbers of postsynaptic dopamine receptors. Together, this is thought to promote reward attenuation with compensatory overeating. Increasing brain dopamine activity with dopamine agonists or reuptake inhibitors leads to weight loss and reduced food intake.

Notably, decreased mesolimbic dopamine levels may specifically contribute to the hyperphagia observed in individuals with impaired leptin-melanocortin signalling. Neurons signalling to mesolimbic brain areas express \( \text{MC4R} \). Receptor stimulation leads to increased dopamine release and turn over in mesolimbic brain areas and decreased food-seeking behaviours and preference for high-fat foods in animals. In the absence of \( \text{MC4R} \) signalling, low dopamine levels and associated hyperphagia would be expected. Indeed, hyperphagia in \( \text{MC4R} \) deficient rats/mice improves with selective restoration of \( \text{MC4R} \) signalling in the mesolimbic system and imaging studies in leptin deficient humans show changes in brain activity in response to leptin substitution predominantly in the dopaminergic brain areas.

Restoration of mesolimbic dopamine levels by MPH would conceptually lead to improved control of hedonic feeding and food-seeking behaviours and decreased hyperphagia. In addition to mesolimbic signalling, dopamine inhibits hypothalamic NPY expression and activity and stimulates POMC expression and may therefore affect hypothalamic intake regulation downstream of \( \text{LEPR} \) but upstream of \( \text{MC4R} \). It is also assumed that MPH has direct (via norepinephrine stimulation of energy expenditure) and indirect (via anorexigenic effects of norepinephrine) sympathomimetic effects. Figure 5 depicts hypothesized differences in dopamine levels between individuals with normal weight, individuals affected by overweight/obesity, and individuals treated with MPH.

Low appetite, headaches, stomach ache, and insomnia are the most common side effects of MPH. Accordingly, the majority of the patients in this case series reported an increase in disordered sleep, nervousness, hyperactivity, impulsivity, tics, and headaches after 1 year of MPH use compared with baseline. These differences did not reach significance across the group, and none of the symptoms led to discontinuation of the medication. Additional published adverse
events are increases in blood pressure and heart rate through direct adrenergic effects, but no long-term data on associated increases in cardiovascular risk are available. Furthermore, any potential long-term cardiovascular risk needs to be balanced against the immediate cardiovascular benefits from decreased obesity. We also observed no change in height SDS with MPH use for 1 year. It is described in the literature that the administration of MPH in children with ADHD is associated with a reduction in growth rate. These effects attenuate over time, and data on the effects on final adult height are inconclusive.

We started off-label treatment with MPH on a 2.8-year-old boy with a mutation in the LEPR gene. This young child was characterized
by an excessive weight gain in the first year of life and an extreme feeling of hunger. Since this was a very stressful situation for the parents and the child, and there is no treatment option for patients with a mutation in the leptin receptor gene, we decided after consultation with the head of the paediatric neurology to start the off-label MPH treatment in this boy. The parents did not report any side effects with her child off-label treated with MPH. The BMI showed a stabilization under off-label MPH treatment for the first time. However, parents have decided to control their child’s BMI by consistently controlling child’s lifestyle and stopped off-label MPH treatment after 1.2 years.

The results of this case series have limitations that are inherent to the observational study design, small case number, and short observation period. Because of the observational character of the study, findings may not be generalizable to all patients with LEPR/MC4R mutations. Outcomes, especially on cardiovascular risk profiles after longer use of MPH, will be of interest. A maximal MPH dose of 20 mg/day was used. This dose is lower than the typical dose for ADHD treatment of 1 mg/kg body weight per day or more. It is possible that the use of higher MPH doses would have been associated with greater effects, but possibly also with more pronounced adverse effects.

### Table 1B

| Patient | BMI T0, kg/m² | BMI T1, kg/m² | Δ BMI T0 – T1, kg/m² | BMI SDS T0, SDS | BMI SDS T1, SDS | Δ BMI-SDS before MPH | Δ BMI-SDS T0 – T1 | %BMIP95 T0 | %BMIP95 T1 | Δ %BMIP95 T0 – T1 |
|---------|----------------|----------------|----------------------|----------------|----------------|----------------------|----------------|----------|----------|----------------|
| Patient A | 42.3 | 41 | -1.3 | 3.45 | 3.26 | 0.37 | -0.19 | 191 | 178 | -13 |
| Patient B | 36.5 | 36.3 | -0.2 | 5.39 | 5.01 | 0.24 | -0.38 | 198 | 203 | 5 |
| Patient C | 37.9 | 36 | -1.9 | 3.90 | 3.55 | -0.32 | -0.35 | 194 | 177 | -17 |
| Patient D | 46.8 | 47.5 | 0.7 | 3.86 | 3.83 | 0.62 | -0.03 | 166 | 164 | -2 |
| Patient E | 28.9 | 27.8 | -1.1 | 4.73 | 4.09 | -0.64 | 159 | 153 | -6 |
| Mean ± SD | 38.5 ± 5.9 | 37.7 ± 6.4 | -0.7 ± 0.9 | 4.3 ± 0.7 | 3.9 ± 0.6 | 0.18 ± 0.30 | -0.32 ± 0.20 | 182 ± 16 | 175 ± 17 | -6.6 ± 7.8 |

Abbreviations: BMI, body mass index; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MPH, methylphenidate; SD, standard deviation; SDS, standard deviation score; T0, initiation of MPH; T1, 1-y follow-up.

*P < .05.

**Figure 4** Boxplots of body mass index standard deviation score (BMI-SDS) velocity before (unfilled squares) and during the year of off-label methylphenidate treatment (filled squares) in n = 5 patients with severe obesity due to mutations in the leptin receptor (LEPR) or melanocortin 4 receptor (MC4R) gene (*P < .05)

**Figure 5** Differences in the regulation of dopamine levels in the pre-synaptic cell as well as in the synaptic cleft in individuals with normal weight, in individuals affected by overweight/obesity and in individuals treated with methylphenidate (DAT, dopamine transporter protein; MPH, methylphenidate)
The search for a pharmacological treatment option for patients with monogenic obesity is of immediate interest. Very recently, it has been reported that patients with LEPR mutations can be treated successfully with a specific melanocortin receptor agonist, setmelanotide. To date, setmelanotide is available only within clinical studies and only for patients older than 6 years of age. Long-term data that show the effect of setmelanotide on BMI in patients with LEPR mutations are not available. These and the corresponding approval must be awaited.

In conclusion, our results show that an off-label individual treatment with MPH for 1 year may improve weight trajectory, decrease appetite, and favourably effect eating behaviour in children with LEPR/MC4R deficiency. These results correlate well with the reported anorexic effect of MPH in children and adolescents with ADHD and are plausibly explained by the mechanism of action of MPH. A decrease or even a stabilization of BMI-SDS is highly meaningful in this group of patients, since the natural trajectory would be associated with rapid weight gain leading to obesity complications in short time. However long-term effects, especially on cardiometabolic risk profiles, are unknown.

ACKNOWLEDGEMENTS

We thank Andrea Lüngen (paediatric endocrine nurse) for her contribution to the collection of patient data.

AUTHOR CONTRIBUTIONS

S.B. researched data and wrote the manuscript. J.V.S. and B.L. researched data and reviewed/editied the manuscript. K.K. and H.V. collected patient's data. C.D. reviewed/editied the manuscript. H.B. and J.H. researched data and reviewed/editied the manuscript. M.W. researched data and wrote the manuscript. All authors had final approval of the submitted and published versions.

CONFLICT OF INTEREST STATEMENT

No conflict of interest was declared.

FUNDING INFORMATION

Stephanie Brandt and Julia von Schnurbein received financial support in the form of a research grant from the Hertha-Nathorff-Programm of the Medical Faculty of the University of Ulm (LSSH1000.07; KSKI 002.1).

ORCID

Stephanie Brandt https://orcid.org/0000-0002-8693-2647

REFERENCES

1. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O’Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003;348(12):1085-1095.
2. Vollbach H, Brandt S, Lahr G, et al. Prevalence and phenotypic characterization of MC4R variants in a large pediatric cohort. Int J Obes (Lond). 2017;41(1):13-22.
3. O’Rahilly S, Farooqi IS. Human obesity as a heritable disorder of the central control of energy balance. Int J Obes (Lond). 2008;32(Suppl 7): S55-S61.
4. Funcke JB, von Schnurbein J, Lennerz B, et al. Monogenic forms of childhood obesity due to mutations in the leptin gene. Mol Cellular Pediatr. 2014;1(1):3.
5. Wabitsch M, Funcke JB, von Schnurbein J, et al. Severe early-onset obesity due to bioinactive leptin caused by a p.N103K Mutation in the Leptin Gene. J Clin Endocrinol Metab. 2015;100(9):3227-3230.
6. Wabitsch M, Funcke JB, Lennerz B, et al. Biologically inactive leptin and early-onset extreme obesity. N Engl J Med. 2015;372(1):48-54.
7. Kuhnen P, Clement K, Wiegand S, et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. N Engl J Med. 2016;375(3):240-246.
8. Farooqi IS, O’Rahilly S. 20 years of leptin: human disorders of leptin action. J Endocrinol. 2014;223(1):T63-T70.
9. Valentin JP, Wiedemann E, Humphreys MH. Natriuretic properties of melanocyte-stimulating hormones. J Cardiovasc Pharmacol. 1993;22(2):S114-S118.
10. Sedbazar U, Ayush E, Maejima Y, Yada T. Neuropeptide Y and a-melanocyte-stimulating hormone reciprocally regulate nesfatin-1 neurons in the paraventricular nucleus of the hypothalamus. Neuroreport. 2014;25(18):1453-1458.
11. Harrold JA, Widdowson PS, Williams G. beta-MSH: a functional ligand that regulated energy homeostasis via hypothalamic MC4-R? Peptides. 2003;24(3):397-405.
12. Kohlsdorf K, Nunziata A, Funcke JB, et al. Early childhood BMI trajectories in monogenic obesity due to leptin, leptin receptor, and melanocortin 4 receptor deficiency. Int J Obes (Lond). 2018;42(9):1602-1609.
13. von Schnurbein J, Moss A, Nagel SA, et al. Leptin substitution results in the induction of menstrual cycles in an adolescent with leptin deficiency and hypogonadotropic hypogonadism. Horm Res Paediatr. 2012;77(2):127-133.
14. Nunziata A, Funcke JB, Borck G, et al. Functional and phenotypic characteristics of human leptin receptor mutations. J Endocrine Soc. 2019;3(1):27-41.
15. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med. 1999;341(12):879-884.
16. Willsens T, McMurrath K, Stein M, Lerner M, Spencer T, Wolraich M. ADHD treatment with once-daily OROS methylphenidate: final results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry. 2005;44(10):1015-1023.
17. Schertz M, Adesman AR, Alfierri NE, Belenkowski RS. Predictors of weight loss in children with attention deficit hyperactivity disorder treated with stimulant medication. Pediatrics. 1996;98(4 Pt 1): 763-769.
18. Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F, Zardoya-Santos P. Effects of osmotic-release methylphenidate on height and weight in children with attention-deficit hyperactivity disorder (ADHD) following up to four years of treatment. J Child Neurol. 2012; 27(5):604-609.
19. Landgren M, Nasic S, Johnson M, Lovoll T, Holmgren D, Fernell E. Blood pressure and anthropometry in children treated with stimulants: a longitudinal cohort study with an individual approach. Neuropsychiatr Dis Treat. 2017;13:499-506.
20. Poulton AS, Bui Q, Melzer E, Evans R. Stimulant medication effects on growth and bone age in children with attention-deficit/hyperactivity disorder: a prospective cohort study. Int Clin Psychopharmacol. 2016;31(2):93-99.

21. Albayrak O, Allbrecht B, Scherag S, Barth N, Hinney A, Hebebrand J. Successful methylphenidate treatment of early onset extreme obesity in a child with a melanocortin-4 receptor gene mutation and attention deficit/hyperactivity disorder. Eur J Pharmacol. 2011;660(1):165-170.

22. Wardle J, Guthrie CA, Sanderson S, Rapoport L. Development of the Children's Eating Behaviour Questionnaire. J Child Psychol Psychiatry. 2001;42(7):963-970.

23. Kromeyer-Hauschild K, Kunze D, Wabitsch M. Perzentile für den Body-Mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatsschr Kinderheilkd. 2001;149(8):807-818.

24. Freedman DS, Butte NF, Taveras EM, Goodman AB, Ogden CL, Blanck HM. The limitations of transforming very high body mass indexes into z-scores among 8.7 million 2- to 4-year-old children. J Pediatr. 2017;188:50-56, e1.

25. Freedman DS, Butte NF, Taveras EM, et al. BMI z-scores are a poor indicator of adiposity among 2- to 19-year-olds with very high BMIs, NHANES 1999-2000 to 2013-2014. Obesity (Silver Spring). 2017;25(4):739-746.

26. Tanner JM. The assessment of growth and development in children. Arch Dis Child. 1952;27(131):10-33.

27. Clement K, Biebergart H, Farooqi IS, et al. MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency. Nat Med. 2018;24(5):551-555.

28. Brams M, Mao AR, Doyle RL. Onset of efficacy of long-acting psychostimulants in pediatric attention-deficit/hyperactivity disorder. Postgrad Med. 2008;120(3):69-88.

29. Findling RL, Wigal SB, Bukstein OG, et al. Long-term tolerability of the methylphenidate transdermal system in pediatric attention-deficit/hyperactivity disorder: a multicenter, prospective, 12-month, open-label, uncontrolled, phase III extension of four clinical trials. Clin Ther. 2009;31(8):1844-1855.

30. Lee J, Grizenko N, Bhat V, Sengupta S, Polotskaia A, Joober R. Relation between therapeutic response and side effects induced by methylphenidate as observed by parents and teachers of children with ADHD. BMC Psychiatry. 2011;11(1):70.

31. Sanchez U, Weisszub G, Santos JL, Corvalan C, Uauy R. GCOS cohort: children's eating behavior scores and BMI. Eur J Clin Nutr. 2016;70(8):925-928.

32. Biederman J, Faraone SV, Monuteaux MC, Plunkett EA, Gifford J, Findling RL, Wigal SB, Bukstein OG, et al. Long-term tolerability of methylphenidate treatment of early onset extreme obesity in a child with a melanocortin-4 receptor gene mutation and attention deficit/hyperactivity disorder. Eur J Pharmacol. 2011;660(1):165-170.

33. Volkow ND, Wang GJ, Fowler JS, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci. Off. J. Soc. Neurosci. 2001;21(2):Rc121.

34. Volkow ND, Wang GJ, Fowler JS, et al. Dopamine transporter occupancy in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry. 1998;155(10):1325-1331.

35. Davis C, Levitan RD, Kaplan AS, et al. Dopamine transporter gene (DAT1) associated with appetite suppression to methylphenidate in a case-control study of binge eating disorder. Neuropsychopharmacol: Am College Neuropsychopharmacol. 2007;32(10):2199-2206.

36. Roseberry AG, Stuhman K, Dunigan AL. Regulation of the mesocorticolimbic and mesostriatal dopamine systems by alpha-melanocyte stimulating hormone and agouti-related protein. Neurosci Biobehav Rev. 2015;56:15-25.

37. Bina KG, Cincotta AH. Dopaminergic agonists normalize elevated hypothalamic neuropeptide Y and corticotropin-releasing hormone, body weight gain, and hyperglycemia in ob/ob mice. Neuroendocrinol. 2000;71(1):68-78.

38. Curtis C, Davis C. A qualitative study of binge eating and obesity from an addiction perspective. Eat Disord. 2014;22(1):19-32.

39. Volkow ND, Wang GJ, Fowler JS, et al. Dopamine transporter occupancy in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry. 1998;155(10):1325-1331.

40. Davis C, Levitan RD, Kaplan AS, et al. Dopamine transporter gene (DAT1) associated with appetite suppression to methylphenidate in a case-control study of binge eating disorder. Neuropsychopharmacol: Am College Neuropsychopharmacol. 2007;32(10):2199-2206.

41. Roseberry AG, Stuhman K, Dunigan AL. Regulation of the mesocorticolimbic and mesostriatal dopamine systems by alpha-melanocyte stimulating hormone and agouti-related protein. Neurosci Biobehav Rev. 2015;56:15-25.

42. Bina KG, Cincotta AH. Dopaminergic agonists normalize elevated hypothalamic neuropeptide Y and corticotropin-releasing hormone, body weight gain, and hyperglycemia in ob/ob mice. Neuroendocrinol. 2000;71(1):68-78.

43. Curtis C, Davis C. A qualitative study of binge eating and obesity from an addiction perspective. Eat Disord. 2014;22(1):19-32.

44. Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci. 2011;15(1):37-46.

45. Epstein LH, Temple JL, Neaderhiser BJ, Salis RJ, Erbe RW, Lddy JJ. Food reinforcement, the dopamine D2 receptor genotype, and energy intake in obese and nonobese humans. Behav Neurosci. 2007;121(5):877-886.

46. Samapa P, Runnennik L, Grippo JF. The melanocortin receptor MCR4 controls fat consumption. Regul Pept. 2003;113(1-3):85-88.

47. Cui H, Lutter M. The expression of MCR4s in D1R neurons regulates food intake and locomotor sensitization to cocaine. Genes Brain Behav. 2013;12(6):658-665.

48. Frank S, Heni M, Moss A, et al. Leptin therapy in a congenital leptin-deficient patient leads to acute and long-term changes in homeostatic, reward, and food-related brain areas. J Clin Endocrinol Metab. 2011;96(8):E1283-E1287.

49. Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. Science. 2007;317(5843):1355.

50. Storebo OJ, Pedersen N, Ramstad E, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents—assessment of adverse events in non-randomised studies. Cochrane Database Syst Rev. 2018;5: Cd012069. https://doi.org/10.1002/14651858.CD012069.pub2.

51. Antel J, Albayrak O, Heusch G, Banaschewski T, Hebebrand J. Assessment of potential cardiovascular risks of methylphenidate in comparison with sibutramine: do we need a SCOUT (trial)? Eur Arch Psychiatry Clin Neurosci. 2015;265(3):233-247.

52. Rodrigues AN, Abreu GR, Resende RS, Goncalves WL, Gouvea SA. Cardiovascular risk factor investigation: a pediatric issue. Int J Gen Med. 2013;6:57-66.

53. Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants or stimulant deficiency improves feeling of satiety and reduces BMI-SDS—A case series. Pediatric Obesity. 2020;15:e12577. https://doi.org/10.1111/jipo.12577

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.