NHS England

Evidence review: Metreleptin for Congenital Leptin Deficiency

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First published: July 2017

Updated: Not applicable

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1 Contents

2 Introduction

2.1 Condition

Leptin is a hormone derived from adipose tissue which plays an important role in the suppression of appetite and in energy balance. In normal individuals, serum leptin levels are positively correlated with the mass of adipose tissue. In individuals with congenital leptin deficiency, first described by Montague et al., 1997, the appetite moderating role of leptin is compromised, leading to hyperphagia and early-onset obesity. Affected individuals develop abnormal behaviour around eating, such as hiding food, secretiveness about eating and fighting over food. Whereas most obese individuals exhibit high levels of serum leptin, those with congenital leptin deficiency have undetectable levels. The condition is also associated with increased risk of infections due to impaired T-cell mediated immunity, hyperinsulinaemia, hypothalamic hypothyroidism and hypogonadotropic hypogonadism leading to pubertal absence. In addition to these, complications commonly seen in obese individuals may be observed, such as type 2 diabetes, sleep apnoea and advanced bone age. High mortality in childhood and adolescence is observed amongst untreated individuals with the condition.

Since first being described by Montague et al in 1997, a total of twenty individuals with congenital leptin deficiency had been identified as at 2011. These consisted of twelve Pakistani cases, five Turkish cases, two Egyptian cases and one Austrian case (Paz-Filho et al., 2011). A high death rate has been noted amongst cases due to sepsis in childhood, with five of the previously mentioned cases having died (not including seven deaths amongst undiagnosed suspected cases in the same period). A mortality rate amongst leptin-deficient patients of at least 20% has been suggested based on these numbers (Paz-Filho et al., 2011).

2.2 Intervention

Metreleptin is a synthetic, recombinant analogue of leptin produced using E. coli bacteria. Successful treatment leads to significant weight loss and reversal of certain comorbidities. There is no alternative treatment currently available and conventional weight loss interventions are ineffective, with bariatric surgery being contraindicated due to the high level of risk and likely ineffectiveness amongst this patient group.

The treatment is administered subcutaneously, twice daily and continues for the lifetime of the patient. Dosage may vary depending on age, weight, gender and clinical response to treatment.

A licensing application has been submitted in the EU for metreleptin to be used to treat complications of leptin deficiency in patients with congenital or acquired generalised lipodystrophy and in a subset of patients with partial lipodystrophy. Following marketing authorisation, use for congenital leptin deficiency would be classed as an off-label use of an approved medication. Currently metreleptin is provided free of charge by Aegerion Pharmaceuticals as part of a named patient programme for compassionate use.

3 Summary of results

- This evidence review found seven before-after case studies of metreleptin in individuals with congenital leptin deficiency. The most commonly reported outcomes were various measures of weight reduction, generally reported as either Body Mass Index (BMI) scores or equivalent Z scores where reported for children.
- The largest (n=4) study by Paz-Filho et al. (2010) also reported the longest follow-up period of 10 years. However only the effects of treatment withdrawal were observed at this time point.
- The majority of studies reported far shorter follow-up periods, this being approximately two years on average. However this is complicated by the fact that different outcome measures were measured after different periods of follow-up.
- All studies included in this review reported significant degrees of weight loss amongst both adult and child participants. Amongst 3 adults of Turkish origin with leptin deficiency, Paz-Filho et al. (2010) found a mean reduction from baseline BMI of 51.2 kg/m^2 to 26.9 kg/m^2 after 18 months. This represents a change in BMI classification from class 3 obesity to overweight.
- Studies by Paz-Filho et al. (2008a), von Schnurbein et al. (2012 & 2013) and Wabitsch et al. (2015a & 2015b) all reported weight loss in children resulting in the equivalent annual reduction in Z score of between 1.03 (Paz-Filho, 2008a) and 2.62 (Wabitsch et al., 2015b).
- Several comorbidities and associated proxy measures were reported, including glucose metabolism, lipid metabolism, cognitive development and reproductive function.
- One paper by Paz-Filho et al. (2010) reported the resolution of type 2 diabetes in a woman with congenital leptin deficiency and the normalisation of blood glucose and insulin levels in three other participants.
- Two studies identified the effects of leptin replacement therapy on reproductive function.
- Von Schnurbein et al. (2012) identified that treatment with metreleptin lead to fast progression of pubertal development in a teenaged Austrian girl suffering from hypogonadotropic hypogonadism associated with her congenital leptin deficiency.
- Paz-Filho et al. (2010) reported the development of regular menstrual periods in two female adults and normalisation of testosterone levels in one adult male. Before treatment the participants were hypogonadic, however all developed full secondary sexual characteristics and normal sexual function.
- Improvements were also noted in the cognitive development of a five year old boy by Paz-Filho (2008a). Measures of cognitive ability indicated that the case's level of ability had increased from baseline measurements placing them in the 4th percentile, this rose to the 14th percentile for verbal scores and the 30th percentile for nonverbal scores after 25 months of treatment (these values being considered within the normal range).
- The studies included are of variable quality and suffer a number of limitations. These include extremely small sample sizes, lack of controls, lack of methodological information, unclear or inconsistent reporting of outcomes, lack of information on treatment adherence and lack of patient safety information.
- No studies reported quality of life outcome measures or cost-effectiveness.
- No comparisons were made to other treatment options or to standard care, meaning that it cannot be certain that changes post receiving treatment were due to metreleptin or due to the natural course of the disease. However this appears unlikely based on the well understood mechanism of leptin on appetite.
- Despite the issues with the evidence base, findings are broadly consistent across different studies. Most of the improvements in outcomes reflect plausible mechanisms of action based on what is known about obesity and/or the effects of leptin.
- The published literature on the use of metreleptin to treat congenital leptin deficiency is limited, this is unavoidable due to the rarity of the condition. The available evidence does not preclude its use but is too limited to make blanket recommendations.

4 Methodology

- The methodology was in accordance with NHS England Specialised Services Methods for Evidence Review.
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Highly Specialised Services team for the topic (see section 9).
- The PICO was used to search for relevant publications in the following sources: EMBASE and MEDLINE (see section 10 for search strategy).
- The search dates for publications were between 1st January 2007 and 16th March 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).
- In some instances, z scores and mean values have been calculated by the authors of this review to aid in the interpretation of results. This is noted in the text when performed and these calculated figures are not included in the review's evidence tables.

5 Results

In total, seven published studies were identified for inclusion in this evidence review. However, it should be noted that there is overlap amongst these studies in terms of the included participants. A table illustrating this overlap can be seen in Appendix 1: Study Participant Overlap and these are mentioned within the text where relevant.

Because of the significant overlap between two particular studies by Paz-Filho et al. (2008b & 2010), in terms of the participants included, the outcome measures and the time-frame, Paz-Filho's et al. earlier paper (2008b) was excluded from the review based on comments received during consultation. Paz-Filho et al. 2008b is primarily focused on the effects of leptin treatment on blood glucose and insulin response, these being proxy markers for risk of type 2 diabetes mellitus. A selection of these outcomes of more direct relevance to the questions being asked by this review is reported by Paz-Filho et al. 2010.

No cost-effectiveness studies or studies investigating health-related quality of life were found.

All studies of this rare condition had extremely small numbers of participants. Study designs were limited by the small number of cases, meaning that before-after designs were used. None of the studies had strict controls (beyond population comparators), randomisation or blinding. To bolster the evidence for a causal relationship with metreleptin, some studies incorporated short periods of treatment withdrawal.

Several studies report a statistic known as a Z score. Z scores (also known as Standard Deviation Scores) are used to show how BMI measurements differ from age and sex specific averages. They provide a way of comparing BMI across age groups despite there being normal differences in BMI as individuals grow and develop. A value of zero would indicate that the participant had a normal BMI for their age whereas a value of 3 would indicate that they were in the top 99.9th percentile for their age (or 3 standard deviations away from the average).

Full details of the study designs and outcomes are summarised in the evidence tables in section 8.

5.1 Is metreleptin a clinically effective treatment for obesity caused by congenital leptin deficiency when compared to normal treatment?

- None of the included studies were comparative in nature, exclusively reporting on the same patients' outcomes at baseline and at follow-up. Paz-Filho et al. 2010 reported on the effects of stopping and restarting treatment but this is not considered to be comparative by the reviewer.
- All of the included studies identified reductions in Body Mass Index following treatment with metreleptin. Reduction in Body Mass Index is the primary measure of clinical effectiveness considered by this review, with other obesity related comorbidities discussed later in this review.
- Overall, the size of these weight reductions was clinically important. Representing transitions across obesity risk categories.
- There was a lack of statistical analysis in studies to identify the probability of this being due to chance.
- Weight-loss was generally rapid following the commencement of treatment.
- The amount of weight lost was variable, presumably in part due to the heterogenous nature of the participants included in the trials in terms of age, sex and ethnicity and cultural background as well as in differences in treatment dosage and administration.
- Whether weight-loss was maintained in the long-term is not discernible due to the short follow-up periods in the included studies.

5.1.1 Body Mass Index (Adult)

- Following 8 weeks of treatment, Wabitsch et al. (2015a) found that two 2 German siblings, aged nine and six respectively, saw BMI reductions from 39.6kg/m^2 to 35.8kg/m^2 and from 35.2kg/m^2 to 31.7kg/m^2 following treatment with metreleptin. This represents a change in z scores from 3.5 to 3.3 and from 4.1 to 3.8 respectively.
- Amongst 3 adults of Turkish origin with leptin deficiency, Paz-Filho et al. (2010) found a mean reduction from baseline BMI of 51.2 kg/m^2 to 26.9 kg/m^2 after 18 months, at which point weight stabilised. This represents a change in BMI classification from class 3 obesity to overweight.
- The use of Dual-Energy X-Ray Absorptiometry (DXA) allowed Paz-Filho et al. (2010) to identify that the majority of weight-loss was due to reduction in fat mass.

5.1.2 Weight Regain

- To reinforce their findings, Paz-Filho et al. (2010) reported on brief periods of treatment withdrawal into their study. During the 4th, 5th, and 6th year of treatment, adults had leptin withheld for 6 weeks, leading to substantial weight gain (mean average of 5.7 kg calculated by the reviewer based on reported figures).

5.1.3 Body Mass Index (Child)

- Paz-Filho et al. (2010) reported the effects of treatment on a male child from the same Turkish family. The boy saw a reduction in BMI from a pre-treatment baseline of 39.6 kg/m^2 at age 5, to 22.6 kg/m^2 at age 9. No BMI Z scores were provided for this child and height information was not reported to allow their calculation, making comparison difficult.
- Wabitsch et al. (2015b) reported on a 9 month old male born to two healthy, normal-weight Turkish parents with known consanguinity. The patient saw a reduction in BMI from a baseline value of 44.8 kg/m^2 (z = 5.9) to 34.2 kg/m^2 (z = 5.0) after 18 weeks of treatment.
- Paz-Filho et al. (2008a) investigated a 7-year-old male born to a highly consanguineous Turkish family. The patient saw a reduction in BMI from a baseline value of 39.6 kg/m^2 to 23.8 kg/m^2 after 25 months. Z scores were not provided but were calculated as z = 4.48 at baseline and z = 2.43 after 24 months of treatment.
- Two studies by von Schnurbein et al. (2012) looked at the effects of metreleptin treatment on a teenaged Austrian girl, reporting reductions from a baseline BMI of 35.9 kg/m^2 (z = 3.04) to 26.9 kg/m^2 (z = 1.73) after 62 weeks of treatment. There is some discrepancy in the figures presented by von Schnurbein's et al. 2012 and 2013 papers respectively, with the former reporting a baseline BMI of 35.4 kg/m^2 and the latter reporting a baseline BMI of 35.9 kg/m^2. No comment on the reason for this difference is made by the authors.

Table 1: Summary of reported BMI Z-scores

Z Score			Months Follow-Up	Z Score Reduction per annum	Start Age of Participant	Author
Start	End	Change				
4.48*	2.43*	-2.05	24.0	-1.03	5y1m	Paz-Filho et al., 2008a
3.04**	1.73**	-1.31	14.3	-1.10	14y9m	von Schnurbein et al., 2012
						von Schnurbein et al., 2013
3.5	3.3	-0.2	1.85	-1.30	9y9m	Wabitsch et al., 2015a
4.1	3.8	-0.3	1.85	-1.95	6y4m	

5.9	5.0	-0.9	4.1	-2.62	3y1m	Wabitsch et al., 2015b

** Z scores were not reported in the original paper but have been calculated by the reviewer using reported height, weight and age information*
***Reported as Standard Deviation Scores in the original papers, these are equivalent to Z scores*
N.B. Two remaining papers did not provide sufficient information on their participants to enable calculation of z scores

5.2 Is metreleptin a cost effective treatment for obesity caused by congenital leptin deficiency when compared to normal treatment?

- No studies were identified which investigated the cost-effectiveness of metreleptin treatment for congenital leptin deficiency.

5.3 Does treatment with metreleptin present any significant patient safety concerns?

- None of the studies included in this review reported on adverse events or patient safety incidents.
- Caution should be exercised when interpreting the lack of reported incidents. It is not clear whether results were omitted due to a total lack of safety issues or because any incidents which may have occurred were not reported by study authors.
- Similarly, the effects of long-term, continuous use of metreleptin cannot be discerned based on the papers selected for inclusion in this evidence review.

5.4 Does treatment with metreleptin lead to resolution of the comorbidities commonly associated with congenital leptin deficiency?

- Resolution of comorbidities or the reduction of disease risk factors were reported by several studies. These are discussed in detail below.
- The long-term effectiveness of metreleptin with regards to resolving comorbidities or reducing measures of disease risk is unknown.

5.4.1 Glucose Metabolism

- Paz-Filho et al. (2010) reported that leptin replacement therapy normalised serum glucose and insulin levels amongst participants and that this lead to the resolution of type 2 diabetes in one adult, female patient.
- Wabitsch et al. (2015b) found that after 18 weeks, metreleptin therapy lead to a reduction in insulin levels from 19.2 mU/litre to 4.8 mU/litre in a 7 -year-old male born to a highly consanguineous Turkish family. The clinical implication of this reduction is not clear and is not discussed by the authors of the study.
- Paz-Filho et al. (2008a) reported that a 7 year old born to a highly consanguineous Turkish family presented with hyperinsulinemia[1] before treatment. This normalised as their weight decreased, moving from 21 uU/ml to 7 uU/ml.
- von Schnurbein et al. (2013) quantified the reduction in insulin resistance of an Austrian teenaged girl. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) reduced from a baseline value of 10.7 to 6.0. This still does not fall within the healthy range of 0.5–1.4 however the follow-up period of the study was limited to 62 weeks.

5.4.2 Reproductive Function

- In a teenaged Austrian girl suffering from hypogonadotropic hypogonadism[2] associated with her congenital leptin deficiency, von Schnurbein et al. (2012) identified that treatment

[1] Excess levels of insulin circulating in the blood relative to the level of glucose
[2] Diminished functional activity of the ovaries, due to the impaired secretion of hormones, leading to delayed, reduced, or absent puberty

with metreleptin lead to fast progression of pubertal development and the induction of menstruation.

- The progression of reproductive development in three congenitally leptin deficient adults was discussed by Paz-Filho et al. (2010). Before treatment, the participants were hypogonadic. After treatment, menstrual periods became regular in both female adults and the male adult's testosterone and free testosterone levels reached normal values. All adults fully developed secondary sexual characteristics and developed normal sexual function.

5.4.3 Cognitive Development

- Paz-Filho et al. (2008a) examined cognitive development in a five year old boy being treated with r-metHuLeptin for leptin deficiency. The case was evaluated at baseline (aged 5y1m) and then subsequently at 5y11m (ten months after treatment initiation) and 7y2m (25 months after treatment initiation).
- Cognitive ability was evaluated using Differential Ability Scales (DAS)[3]
- The patient's pre and post treatment DAS verbal and nonverbal scores were lower than the scores for age matched controls from a normative sample.
- Treatment was followed by an upward trend in development, with scores generally normalising after 25 months.
- Pre-treatment verbal and nonverbal scores were in the 4th percentile.
- At 10 months, verbal scores were in the 9th percentile while nonverbal scores were in the 6th percentile.
- By 25 months, the patient's verbal scores were in the 14th percentile while his nonverbal scores were in the 30th percentile (both broadly within normal limits for that age).
- NEPSY (A Developmental NEuroPSYchological Assessment) was used to evaluate neuropsychological functioning.[4]
- The patient's intra-treatment rate of development showed an increasing trend compared to his pre-treatment rate of development, at 25 months many rate of development measures matched or exceeded age expectations.

5.4.4 Lipid Metabolism

- Paz-Filho et al. (2010) reported on various lipid markers relating to the treatment of a cohort of three Turkish origin adults and one child. Mean averages have been calculated by the reviewer based on the reported patient level values.
- For total cholesterol, a mean average pre-treatment baseline value of 149.8 mg/dL was calculated from the reported papers by the reviewer, decreasing to 121.5 mg/dL after 18 months of treatment. This indicates a change from borderline high to near optimal.
- For High Density Lipoprotein (HDL) cholesterol, a mean average pre-treatment baseline of 32.8 mg/dL was observed, increasing to 52.0 mg/dL after 18 months of treatment. This indicates a change in risk of heart disease from increased to normal.
- For Low Density Lipoprotein (LDL) cholesterol, a mean average pre-treatment baseline of 83.5 mg/dL was reported, decreasing to 52.0 mg/dL after 24 months of treatment. This indicates a small improvement but does not represent a change in risk category which remains in the optimal range <100 mg/dL.
- For triglycerides, a mean average pre-treatment baseline of 166.8 mg/dL was reported, decreasing to 87.8 mg/dL after 18 months of treatment. This indicates a change in category from borderline high to desirable.

[3] A collection of cognitive and achievement tests developed in the United States
[4] A series of tests in six functional domains, used in various combinations to assess neuropsychological development in children aged 3–16 years

- Wabitsch et al. (2015b) observed reductions in triglycerides in a 9 month old male child born to Turkish parents with known consanguinity and treated with metreleptin. Starting at a baseline of 177.1 mg/dL (indicating high risk of heart disease) and falling to 35.4 mg/dL after 18 months of treatment (indicating an acceptable level of risk in this age group).
- Paz-Filho et al. (2008a) reported on a 7 year old male born to a highly consanguineous Turkish family. After 25 months of treatment, this case experienced improvements in blood lipid levels, however only HDL cholesterol improved to the degree that a risk categorisation was reduced.
- Total cholesterol reduced from 166 mg/dL (desirable) to 155 mg/dL (desirable but improved).
- LDL cholesterol reduced from 87 mg/dL (Optimal) to 66 mg/dL (Optimal but improved).
- HDL cholesterol increased from 36 mg/dL (major risk factor for heart disease) to 65 mg/dL (protective against heart disease).
- Triglycerides decreased from 216 mg/dL (high) to 120 mg/dL (high but improved).

5.4.5 Hepatic Lipids

- Hepatic lipids were measured in a 14 year old Austrian girl by von Schnurbein et al. (2013) using Hydrogen-1 MR spectroscopy (H-MRS).[5]
- Hepatic lipids were raised prior to leptin therapy at 49.7%, decreasing to 9.4% after 15 months. This represents a change equivalent to moving from grade III hepatic steatosis (the highest category of non-alcoholic fatty liver disease) to grade 0 (normal).

5.4.6 Cardiac Risk

- Paz-Filho et al. (2008a) reported blood pressure results for a 7-year-old male born to a highly consanguineous Turkish family. A reduction from 110/70 mmHg to 101/66 mmHg was noted, representing a change from the 90th percentile to within normal limits.

5.5 Do any population sub-groups benefit more than others from treatment for congenital leptin deficiency with metreleptin when compared to normal treatment?

- Congenital leptin deficiency is an extremely rare disease and therefore there are a very small number of individuals living with the condition who have been included in studies.
- Because of this fact, there is a degree of overlap between several of the included studies (see Appendix 1: Study Participant Overlap).
- Where possible, the authors of this review have attempted to identify where individuals have been included in multiple studies and have attempted to ensure that outcomes such as weight-loss are not inflated disproportionately by reporting the same patient's outcomes multiple times.
- A lack of diversity amongst study participants is a factor resulting from the diseases rarity. Many of the patients reported are of Turkish background and are from consanguineous lineages.
- How generalisable the findings found amongst these cases will be to the England population is uncertain.
- One sub-group which may present a greater opportunity to benefit from treatment are those individuals with type 2 diabetes resulting from obesity. This condition attracts significant treatment costs for the lifetime of patients, meaning that medication cost savings may offset treatment costs to some extent. However, without formal evidence

[5] A non-invasive technique for the measurement of hepatic lipid retention (steatosis).

around cost-effectiveness, it is not possible to quantify this.

6 Discussion

6.1 Implications

- Treatment with Metreleptin uniformly lead to clinically meaningful reductions in BMI amongst all study participants. Where investigated further, the majority of this weight-loss was due to reductions in fat mass.
- Treatment with Metreleptin lead to either improvement or resolution of many of the comorbidities associated with obesity caused by congenital leptin deficiency.
- Where tested, the withdrawal of Metreleptin treatment lead to the regain of weight in participants.

6.2 Limitations & Weaknesses

- There was a lack of studies which investigated the cost-effectiveness of Metreleptin for congenital leptin deficiency.
- There was a lack of studies which investigated quality of life outcomes for patients being treated with Metreleptin for congenital leptin deficiency.
- There was a lack of studies which quoted patient safety incidents, treatment adherence and side-effects of treatment.
- Studies all lacked controls, randomisation and blinding.
- Statistical analysis of results was generally lacking.

6.3 Unexpected Findings

- The majority of comorbidities identified are caused by obesity associated with congenital leptin deficiency and not directly caused by a lack of leptin itself.

6.4 Further Research

- Further research should investigate long-term follow-up of patients and potentially systematically reviewing all findings to date, to include a meta-analysis should study heterogeneity not prevent this.
- A focus on reporting patient safety incidents, treatment adherence and side-effects of treatment should be investigated in research going forward.
- Cost-effectiveness studies of metreleptin for congenital leptin deficiency would prove useful to inform the commissioning of the drug for this indication.

7 Conclusion

- Based on the findings of this evidence review, there is evidence of medium quality which indicates that Metreleptin is effective at treating the symptoms of congenital leptin deficiency.
- Regular treatment with metreleptin leads to rapid weight-loss which appears to be well maintained in the short to medium-term time frame.
- In addition to the reduction in excess weight, many of the associated comorbidities such as type 2 diabetes, delayed puberty, non-alcoholic fatty liver disease, high blood pressure and high cholesterol also appear to be positively affected in the small number of participants reported.
- The evidence base is sparse, consists of exclusively before-after design trials and follow-up times are relatively short-term.
- Despite this, findings for the main outcomes of interest are broadly consistent across studies and appear to be consistent with the known mechanism of action for leptin.
- In summary, metreleptin is the only available treatment for congenital leptin deficiency, whilst the evidence base is sparse it is consistent in reporting the effects of metreleptin on weight-loss (and weight-regain when withheld). There is insufficient evidence to make clear recommendations on factors such as patients most likely to benefit from treatment beyond the likelihood of the various sequela of obesity being positively affected however the sheer rarity of the condition may mean that this is less of an issue than in more prevalent conditions.

8 Evidence Summary Table

Use of Metreleptin to treat Congenital Leptin Deficiency									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Wabitsch et al., 2015a	P1-Before-and-after trial	2 German siblings, a 9-year-old girl (patient A) and a 6-year-old boy (patient B) with severe early-onset obesity and hyperphagia delivered to normal weight, caucasian parents without known consanguinity	Metreleptin by injection, 0.3 mg per kg of lean body weight daily	Primary Clinical effectiveness	Weight-loss	Following 8 weeks of treatment, Patient A reduced from 77.9kg (BMI 39.6kg/m^2, z = 3.5) to 71.7kg (BMI 35.8kg/m^2, z = 3.3), over the same period of time, Patient B reduced from 50.4kg (BMI 35.2kg/m^2, z = 4.1) to 46.6kg (BMI 31.7kg/m^2, z = 3.8)	3	Direct	Small sample size with no control. Risk of bias due to inherent lack of randomisation and blinding. Primary/Secondary outcomes were not specified. Reported outcomes were predominantly endocrine and metabolic parameters. Subjects had congenital functional leptin deficiency; this differs from congenital leptin deficiency in that there are detectable levels of biologically inactive leptin, potentially limiting generalisability to

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Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									the wider leptin deficient population. Very short term follow-up period of 8 weeks, therefore longer term measures of effectiveness, safety and adherence are not available. A large effect size was reported, with reductions in weight of 6.2kg (8.0%) and 3.8kg (7.5%) over the follow-up period. No statistical analysis performed, p values not reported.
Paz-Filho et al., 2010	P1-Before-and-after trial	3 adults and 1 child of Turkish origin with leptin deficiency:	r-metHuLeptin, beginning at 0.02-0.04 mg/kg/day	Primary Clinical effectiveness	Weight Loss (BMI)	Baseline mean adult BMI was 51.2 ± 2.5 kg/m^2 (51.4, 46.7, and 55.4 kg/m^2, for patients A, B, and C respectively) After 18 months of treatment, a stable mean BMI of 26.9 ± 2.1 kg/m^2 (24.8, 26.1, and 31.3 kg/m^2 for A, B, and C respectively) was reached. The latest BMI as of March 2010 was 29.5 ± 2.8 kg/m^2.	7	Direct	Extensive 10 year follow-up period. No information on safety incidents

<table>
<tr><th colspan="10">Use of Metreleptin to treat Congenital Leptin Deficiency</th></tr>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Intervention</th><th>Outcome measure type</th><th>Outcome measures</th><th>Results</th><th>Quality of Evidence Score</th><th>Applicability</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td></td>
<td></td>
<td>A: Adult male A, 22-year-old,
B: Adult female, 34-year-old
C: Adult female, 30-year-old
D: Child male, 5-year-old</td>
<td>delivered subcutaneously at 6pm each day. Dosage was adjusted to avoid excessively rapid weight-loss in the child. Effects of withdrawal and reinstatement were also evaluated</td>
<td></td>
<td></td>
<td>The boy saw a reduction in BMI, from a baseline of 39.6 kg/m^2 before treatment at age 5, to 22.6 kg/m^2 at age 9.</td>
<td></td>
<td></td>
<td>reported. It isn't clear if this is due to there being no adverse events or if there was no reporting of any that did occur.

Small sample size from a single extended family limits generalisability. No control, risk of bias due to inherent lack of randomisation and blinding.

No statistical analysis performed, p values not reported.

Causality reinforced by withdrawing patients from treatment for a limited time.</td>
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<tr>
<td colspan="5"></td>
<td>Weight Loss (Body Fat Percentage)</td>
<td>Most of the decrease in BMI was attributed to fat mass loss, as measured by Dual-Energy X-Ray Absorptiometry (DXA). In 2001, the initial total body fat percentages were 43.7%, 45.7%, and 49.9% for patients A, B, and C, respectively. In 2007, those percentages were equal to 7.0%, 36.4%, and 45.0%, respectively for patients A, B, and C.</td>
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</tr>
<tr>
<td colspan="5"></td>
<td>Bone Mineral Density</td>
<td>Before treatment, patient A had low bone mineral density (BMD) at the lumbar spine (BMD of L2–L4, 0.924 g/cm^2; T-score -1.96; Z-score -2.36), and the females had normal BMDs at all sites. After 6 years, the male's BMD at the lumbar spine increased by 11% (BMD of L2–L4, 1.042 g/cm^2; T-score -1.5; Z-score -1.1). The females' BMDs remained within normal range, without significant changes.</td>
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<tr>
<td colspan="5"></td>
<td>Weight-regain</td>
<td>During the 4th, 5th, and 6th year of treatment, adults were submitted to brief periods of leptin withdrawal during 6 weeks, leading to substantial weight gain (5.6 ± 3.8 kg for patient A, 5.4 ± 0.9 kg for patient B, and 6.0 ± 2.2 kg for patient C).</td>
<td colspan="3"></td>
</tr>
<tr>
<td colspan="5"></td>
<td>Lipid metabolism</td>
<td>
<table>
<tr><th rowspan="2">Patient</th><th colspan="2">Total Cholesterol (mg/dL)</th></tr>
<tr><th>Before Treatment</th><th>After 18 months</th></tr>
<tr><td>A</td><td>137</td><td>96</td></tr>
<tr><td>B</td><td>115</td><td>110</td></tr>
<tr><td>C</td><td>181</td><td>125</td></tr>
<tr><td>D</td><td>166</td><td>155</td></tr>
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<td colspan="3"></td>
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Use of Metreleptin to treat Congenital Leptin Deficiency

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Intervention</th><th>Outcome measure type</th><th>Outcome measures</th><th>Results</th><th>Quality of Evidence Score</th><th>Applicability</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><th rowspan="2">Patient</th><th colspan="2">HDL-c (mg/dL)</th></tr>
<tr><th>Before Treatment</th><th>After 18 months</th></tr>
<tr><td>A</td><td>29.9</td><td>53.3</td></tr>
<tr><td>B</td><td>36.8</td><td>51.2</td></tr>
<tr><td>C</td><td>28.6</td><td>38.4</td></tr>
<tr><td>D</td><td>36</td><td>65</td></tr>
</table>
<table>
<tr><th rowspan="2">Patient</th><th colspan="2">LDL-c (mg/dL)</th></tr>
<tr><th>Before Treatment</th><th>After 24 months</th></tr>
<tr><td>A</td><td>82</td><td>29</td></tr>
<tr><td>B</td><td>62</td><td>49</td></tr>
<tr><td>C</td><td>103</td><td>64</td></tr>
<tr><td>D</td><td>87</td><td>66</td></tr>
</table>
<table>
<tr><th rowspan="2">Patient</th><th colspan="2">Triglycerides (mg/dL)</th></tr>
<tr><th>Before Treatment</th><th>After 18 months</th></tr>
<tr><td>A</td><td>125</td><td>69</td></tr>
<tr><td>B</td><td>79</td><td>47</td></tr>
<tr><td>C</td><td>247</td><td>115</td></tr>
<tr><td>D</td><td>216</td><td>120</td></tr>
</table>
</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Glucose metabolism</td><td>Patient C was diagnosed with type 2 diabetes. Leptin replacement normalised glucose and insulin levels, ultimately leading to the resolution of type 2 diabetes.
<table>
<tr><th rowspan="2">Patient</th><th colspan="2">Glucose (ng/dL)</th></tr>
<tr><th>Before</th><th>After 18</th></tr>
<tr><td>A</td><td>91</td><td>78</td></tr>
</table>
</td><td></td><td></td><td></td></tr>
</table>

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<table>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>B</td><td>88</td><td>84</td></tr>
<tr><td>C</td><td>131</td><td>86</td></tr>
<tr><td>D</td><td>79</td><td>87</td></tr>
</table>
<table>
<tr><th rowspan="2">Patient</th><th colspan="2">Insulin (uU/mL)</th></tr>
<tr><th>Before</th><th>After 18</th></tr>
<tr><td>A</td><td>4.8</td><td>1.8</td></tr>
<tr><td>B</td><td>3.8</td><td>1.8</td></tr>
<tr><td>C</td><td>7.5</td><td>3.1</td></tr>
<tr><td>D</td><td>21</td><td>7</td></tr>
</table>
</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Reproductive Function</td><td>Before treatment, the adults were hypogonadic. After treatment, menstrual periods became regular in both female adults.
The male adult's testosterone and free testosterone levels reached normal values. All adults fully developed secondary sexual characteristics and developed normal sexual function.</td><td></td><td></td><td></td></tr>
<tr><td>Wabitsch et al., 2015b</td><td>P1-Before-and-after trial</td><td>9 month old male born to two healthy, normal-weight Turkish parents with known consanguinity (first-degree cousins)</td><td>Recombinant human leptin (metreleptin) at an initial dose of 0.03 mg per kilogram of lean body weight per day</td><td>Primary

Clinical effectiveness</td><td>Weight Loss (BMI)</td><td>The patient saw a reduction in BMI from a baseline value of 44.8 kg/m^2 (z = 5.9) to 34.2 kg/m^2 (z = 5) at 18 weeks post treatment.</td><td>6</td><td>Direct</td><td>Single patient study only. Patient has a high level of non-functional circulating leptin, marking them apart from most other cases with extremely low levels of circulating leptin. This may limit generalisability of</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Weight Loss (Fat mass)</td><td>The patient saw a reduction in fat mass from a baseline value of 23.1 kg to 20.5 kg at 9 weeks post treatment.</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Lipid metabolism</td><td>The patient saw a reduction in triglycerides from a baseline value of 177.1 mg/dL to 35.4 mg/dL at 18 weeks post treatment.</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Glucose metabolism</td><td>The patient saw a reduction in insulin levels from a baseline value of 19.2 mU/litre to 4.8 mU/litre at 18 weeks post treatment.</td><td></td><td></td><td></td></tr>
</table>

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<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Intervention</th><th>Outcome measure type</th><th>Outcome measures</th><th>Results</th><th>Quality of Evidence Score</th><th>Applicability</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>the study.

Follow- up period is short (18 weeks).

Small sample size limits the strength and generalisability of findings.</td></tr>
<tr><td>Paz-Filho et al., 2008a</td><td>P1-Before-and-after trial</td><td>7-year-old male born to a highly consanguineous Turkish family (parents are first-degree cousins).</td><td>Recombinant methionyl human leptin (r-metHuLeptin) administered once a day, with a starting dose of 1.36 mg/day. Due to decreased

food intake and subsequent weight loss, dosage was progressively reduced to</td><td>Primary

Clinical effectiveness</td><td>Weight Loss (BMI)</td><td>The patient saw a reduction in BMI from a baseline value of 39.6 kg/m^2 (>97th percentile for same age & sex) to 23.8 kg/m^2 (>97th percentile for same age & sex) at 25 months.</td><td>7</td><td>Direct</td><td>Assumption that the level of cognitive functioning at the pre-treatment evaluation was representative of the patient's cognitive functioning from birth until baseline evaluation.

Language and cultural differences may have introduced biases to the results, although these</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Cardiac Risk</td><td><table><tr><th></th><th>Baseline</th><th>25 Months</th><th>Change</th></tr><tr><td>Systolic BP (mmHg)</td><td>110</td><td>101</td><td>-9</td></tr><tr><td>Diastolic BP (mmHg)</td><td>70</td><td>66</td><td>-4</td></tr></table></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Glucose Metabolism</td><td><table><tr><th></th><th>Baseline</th><th>25 Months</th><th>Change</th></tr><tr><td>Glucose (mg/dl)</td><td>79</td><td>87</td><td>8</td></tr><tr><td>Insulin (uU/ml)</td><td>21</td><td>7</td><td>-14</td></tr></table></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Lipid Metabolism</td><td><table><tr><th></th><th>Baseline</th><th>25 Months</th><th>Change</th></tr><tr><td>Cholesterol (mg/dl)</td><td>166</td><td>155</td><td>-11</td></tr></table></td><td></td><td></td><td></td></tr>
</table>

Use of Metreleptin to treat Congenital Leptin Deficiency									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
			0.45 mg/day			**LDL (mg/dl)** 87 66 -21 **HDL (mg/dl)** 36 65 29 **Triglycerides (mg/dl)** 216 120 -96			should be internally consistent Tools used for neurocognitive assessments were commercially available instruments and potentially not valid for the language and cultural status of the participant
					Cognitive development	DAS (Differential Ability Scales) was used to evaluate general cognitive ability: - The patient's pre- and post- treatment DAS verbal and nonverbal cluster scores were lower than the scores for age- matched controls from the normative sample - Administration of r-metHuLeptin was followed by an upward trend in development, with scores generally normalising by T3. - Pre-treatment verbal and nonverbal scores were in the 4th percentile. At 10 months, verbal scores were in the 9th percentile while nonverbal scores were in the 6th percentile. By 25 months, the patient's verbal scores were in the 14th percentile while his nonverbal scores were in the 30th percentile (both broadly within normal limits for that age). NEPSY (A Developmental NEuroPSYchological Assessment) was used to evaluate neuropsychological functioning: - The patient's intra-treatment rate of development showed an increasing trend compared to his pre-treatment rate of development, at 25 months many rate of development measures matched or exceeded age expectations.			
von Schnurbein et al., 2012	P1-Before-and-after trial	14-year-old, female first child of two healthy, non-obese	Recombinant methionyl human leptin	Primary Clinical effectiveness	Reproductive Function	After 11 weeks, basal and stimulated LH and FSH levels rose to pubertal values. Nocturnal LH and FSH pulsatility were restored. After 45 weeks, uterus volume showed a pubertal size of 20 ml and the LH and FSH nocturnal pulse height rose further with	6	Direct	Single case before-after study limits generalisability.

Use of Metreleptin to treat Congenital Leptin Deficiency									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Austrians without known consanguinity.				frequency remaining roughly the same. After a further 30 weeks of therapy, menstruation occurred at the age of 16 years and 3 months at Tanner stage B4, PH4. IGF1 levels normalised within 11 weeks, and after 45 weeks of therapy, stimulated growth hormone levels were normal at 10.1 µg/l. Pulsatile nocturnal growth hormone showed a normal secretion after 45 weeks of therapy with two pulses over 8 µg/l.			Case is also unusual in being the first patient identified with connatal leptin deficiency in adolescence and also in having a particularly severe form of insulin resistance. This may lead to bias in the reported results. However, case's Western European background and lack of consanguinity presents some benefits in terms of generalisability of results over other papers reviewed. No statistical analysis of results has been performed. 62 week follow up period shows
					Weight-Loss (BMI)	BMI reduced from a baseline value of 35.9 kg/m^2 (3.04 standard deviations) to 26.9 kg/m^2 (1.73 standard deviations) at 62 weeks follow-up.			

Use of Metreleptin to treat Congenital Leptin Deficiency									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									promising results but gives little information on whether these changes will be sustained in the long term. No information given on patient safety and/or acceptability of treatment.
von Schnurbein et al., 2013	P1-Before-and-after trial	14-year-old, female first child of two healthy, non-obese Austrians without known consanguinity.	Recombinant methionyl human leptin	Primary Clinical effectiveness	Weight-Loss (BMI)	BMI reduced from a baseline value of 35.4 kg/m^2 to 26.9 kg/m^2 at 62 weeks follow-up.	6	Direct	Single case before-after study limits generalisability. Case is also unusual in being the first patient identified with connatal leptin deficiency in adolescence and also in having a particularly severe form of insulin resistance. This
					Metabolic Changes	Total cholesterol normalised and LDL cholesterol decreased to within normal range. HDL cholesterol remained decreased at around 0.9 mmol/l. Triglycerides remained persistently elevated (3.0 mmol/l after 62 weeks of treatment). The patient's HOMA-IR decreased from 10.7 to 6.0 and transaminases normalised			
					Hepatic Lipids	Hepatic lipids determined by H-MRS were raised prior to leptin therapy at 49.7%, decreasing to 9.4% after 15 months.			

Use of Metreleptin to treat Congenital Leptin Deficiency									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					Visceral Adiposity	VAT mass dropped under leptin substitution from 3.84 to 1.6 litres after 15 months.			may lead to bias in the reported results. However, case's Western European background and lack of consanguinity presents some benefits in terms of generalisability of results over other papers reviewed. No statistical analysis of results has been performed. 62 week follow up period shows promising results but gives little information on whether these changes will be sustained in the long term. No information given on patient safety and/or

Use of Metreleptin to treat Congenital Leptin Deficiency									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									acceptability of treatment.

9 Grade of Evidence Table

Use of Metreleptin to treat Congenital Leptin Deficiency					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Weight-loss	Wabitsch et al., 2015a	3	Direct	A	Weight gain is one of the primary symptoms of congenital leptin deficiency and is associated with complications commonly seen in obese individuals, such as type 2 diabetes, sleep apnoea and advanced bone age. The findings by Paz-Filho et al (2010) report that three adults reduced from a mean BMI of 51.2 kg/m^2 to one of 26.9 kg/m^2 after 18 months of treatment. This represents a change in classification from class 3 obesity to overweight and compares favourably to the rate of weight-loss seen in bariatric surgery for individuals being treated for normal obesity (Colquitt et al., 2014). However, after ten years the mean BMI value had increased slightly to 29.5 kg/m^2. The boy saw a reduction in BMI, from a baseline of 39.6 kg/m^2 before treatment at age 5, to 22.6 kg/m^2 at age 9. These results suggest that all patients administered metreleptin will see a clinically significant degree of weight loss. However, whether this can be maintained in the long-term is unknown, with some doubt being cast by the increase observed after longer term follow-up. This is not unusual amongst weight-loss interventions in general, where drastic weight-loss is often followed by a degree of regain. All cases reported in the identified papers are either Turkish, German or Austrian in origin, limiting generalisability to the UK population.
	Paz-Filho et al., 2010	7	Direct		
	Wabitsch et al., 2015b	6	Direct		
	Paz-Filho et al., 2008a	7	Direct		
	von Schnurbein et al., 2012	6	Direct		
	von Schnurbein et al., 2013	6	Direct		
Bone Mineral Density	Paz-Filho et al., 2010	7	Direct	B	There is controversy around how obesity may influence Bone Mineral Density (Migliaccio et al., 2010). Low BMD is related to an increased risk of bone fracture. Bone Mineral Density (BMD) was reported by just one study in this review (Paz-Filho et al., 2010). Before treatment, one patient had low BMD of 0.924 g/cm^2 at the lumbar spine whilst two females had normal BMD measurements at all sites. After 6 years, the male participant's BMD at the lumbar spine increased by 11% to 1.042 g/cm^2. The female participants' BMDs remained within normal range, without significant changes. These findings should be interpreted with caution. Findings were reported for a single patient from a single, small, trial. In addition to this, no statistical tests were performed to check the significance of the change. This means that the results may not be applicable to the wider population and could have been caused by chance, bias or confounding.
Lipid Metabolism	Paz-Filho et al., 2010	7	Direct	A	Cholesterol levels are used as an indicator of cardiac and vascular disease

	Paz-Filho et al., 2008a	7	Direct		risk, particularly in the presence of other conditions such as type 2 diabetes. High levels of LDL cholesterol and triglycerides are seen as undesirable, whilst HDL cholesterol has been shown to lend a protective effect, specifically by reducing accumulation of atherosclerosis on artery walls. Changes in blood lipids were reported by Paz-Filho et al (2010) over an 18 or 24 month time period. Before treatment, all patients had low HDL-cholesterol and normal or high triglycerides. Leptin replacement normalised serum lipid levels, with LDL cholesterol reducing on average (mean) by 31.5 mg/dL after 24 months, triglycerides reducing by 79.0 mg/dL over 18 months and HDL increasing by 19.2 mg/dL over 18 months.
	Wabitsch et al., 2015b	6	Direct		
	Paz-Filho et al., 2008a	7	Direct		
	von Schnurbein et al., 2013	6	Direct		
Glucose Metabolism	Paz-Filho et al., 2010	7	Direct	A	Measurements of glucose and insulin provide important information around risk of type 2 diabetes. Type 2 diabetes carries with it significant health impacts for the patient as well as costs to the health system associated with long-term treatment. Reducing the risk of onset of type 2 diabetes is therefore an important outcome, as is resolution of the condition in those who have already acquired it. Paz-Filho et al. (2010) reported that type 2 diabetes was resolved in a 49-year-old female participant after normalisation of blood insulin and glucose levels. Blood glucose and insulin levels were normalised in the remaining three participants also. The study by Paz-Filho et al. (2010) only reported on a single case with type 2 diabetes. This means that the causality of resolution of this condition cannot be attributed to metreleptin for certain. However, taking into account the effects of metreleptin on glucose metabolism amongst other reported cases, the effects of treatment on type 2 diabetes appear plausible.
	Wabitsch et al., 2015b	6	Direct		
	Paz-Filho et al., 2008a	7	Direct		
	von Schnurbein et al., 2013	6	Direct		
Hepatic Lipids	von Schnurbein et al., 2013	6	Direct	B	Fatty liver disease (also known as hepatic steatosis) is a complication of congenital leptin deficiency, also seen in cases of normal obesity. It is associated with the accumulation of fat in the liver, leading to inflammation and in serious cases cirrhosis. The condition is complicated by its relationship with hyperinsulinemia which leads to hepatic insulin resistance. Von Schnurbein et al. (2013) reported outcomes for a single case with non-alcoholic fatty liver disease. Hepatic lipids were high (49.7%) prior to leptin therapy. Within 3 days after the start of leptin therapy, there was a slight but obvious decrease in hepatic lipids to 46.5%, which continued to 24.0% after 3 months and to 9.4% after 15 months. A value of 3.05% is representative of normal-weight 20-29 year old women (Ulbrich et al., 2015). This study does not report if the observed changes are statistically significant and the study is a single-subject, before-after design without controls. It is uncertain therefore how generalisable the findings are. The follow-up time of the study is limited and whether the changes observed are representative of long-term improvements cannot be concluded.

Cardiac Risk	Paz-Filho et al., 2008a	7	Direct	B	Blood pressure is a known risk factor for many diseases, such as heart disease, stroke and kidney failure. Paz-Filho et al. (2008a) reported blood pressure normalisation in a child of Turkish background. At baseline the patient's blood pressure was 110/70 mmHg, just above the 90th percentile for their age. After 25 months of treatment, their blood pressure was normalised, at 101/66 mmHg. As with several of the other studies included in this review, this study describes only a single case, making it difficult to generalise to the wider population of congenital leptin deficient individuals. In addition to this the case is from a consanguineous, Turkish background which may not be as common in England as it is in other European countries. The follow-up period was limited to 25 months meaning evaluation of the long-term impact of treatment is not possible.
Cognitive Development	Paz-Filho et al., 2008a	7	Direct	B	A connection between leptin and cognitive development is hypothesised due to the links between the hormone and several aspects of neural development, including neuron excitability, synaptic plasticity, neural differentiation, migration of neuronal lineage cells to the cortical plate, and regulation of development of hypothalamic feeding (Paz-Filho et al., 2008a). Paz-Filho et al. (2008a) reported that leptin replacement therapy in a 7 year old Turkish child appeared to be associated with changes in rates of development in several neurocognitive domains. The patient's pre- and post- treatment verbal and nonverbal cluster scores were lower than those for age-matched comparators. Treatment was followed by an upward trend in development, with scores generally normalising after two years. Pre-treatment verbal and nonverbal scores were in the 4th percentile. After two years, the patient's verbal scores were in the 14th percentile while his nonverbal scores were in the 30th percentile, both broadly within normal limits for his age. Despite the translation of the test instructions and language based measures, it should be noted that the tests used to measure neurocognitive development in this study may have given biased results due to the patient's cultural background and language. Although this may not affect the internal validity of the study, it presents another issue affecting how generalisable the findings may be. Due to the lack of controls in the study, the patient could only be compared against their own baseline values, it was presumed by the authors that the case's cognitive functioning at pre-treatment evaluation was representative of their cognitive functioning from birth until baseline evaluation. Whilst the authors hypothesis the link between leptin and neuro cognitive development, it is not clear whether there may be other factors contributing towards this, potentially stemming from the known

					consanguinity within the patient's family.
Reproductive Function	Paz-Filho et al., 2010	7	Direct	B	Leptin is known to play a role in pubertal development and progression, acting as a marker of metabolic status and body weight for the hypothalamus to trigger puberty (El-Eshmawy et al., 2010). It can be profoundly distressing for those experiencing it and has implications for fertility. Paz-Filho et al. (2010) reported that before treatment, three adult participants were hypogonadic. After treatment, menstrual periods became regular in both female adults. The male adult's testosterone and free testosterone levels reached normal values. All adults fully developed secondary sexual characteristics and developed normal sexual function. As with all studies included in this review, the small number of cases does make it extremely challenging to generalise to the wider population of those with congenital leptin deficiency. That being said, the effects of leptin upon pubertal development are known in the wider literature and the association between metreleptin treatment and pubertal onset is biologically plausible.
	von Schnurbein et al., 2012	6	Direct		

10 Literature Search Terms

<table>
<tr><td colspan="2">Search strategy Indicate all terms to be used in the search</td></tr>
<tr><td>P – Patients / Population

Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</td><td>Children and adults with congenital leptin deficiency</td></tr>
<tr><td>I – Intervention

Which intervention, treatment or approach should be used?</td><td>Metreleptin (UNII: TL60C27RLH)</td></tr>
<tr><td>C – Comparison

What is/are the main alternative/s to compare with the intervention being considered?</td><td>Normal care</td></tr>
<tr><td>O – Outcomes

What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission</td><td><u>Critical to decision-making:</u>

• Mortality
• Cost effectiveness
• Weight-loss
• Resolution of comorbidities
• Patient safety (complications and adverse effects)
<u>Important to decision-making:</u>

• Quality of Life
• Long term treatment adherence</td></tr>
<tr><td colspan="2">Assumptions / limits applied to search</td></tr>
<tr><td colspan="2">English language, peer-reviewed studies published in journals in the last 10 years. Systematic reviews and RCTs to be prioritised but study designs further down the hierarchy of evidence to be considered based on the quality and volume of papers identified.</td></tr>
</table>

11 Search Strategy

1 ("congenital leptin deficienc*").ti,ab 66
2 exp "LEPTIN DEFICIENCY"/ 457
3 (1 OR 2) 496
4 ("leptin deficienc*").ti,ab 683
5 (3 OR 4) 863
6 (congenital).ti,ab 252652
7 exp "CONGENITAL DISORDER"/ 1225023
8 (6 OR 7) 1302025
9 (5 AND 8) 136
10 (1 OR 3 OR 9) 515
11 (metreleptin).ti,ab 133
12 exp METRELEPTIN/ 235
13 (11 OR 12) 247
14 (10 AND 13) 55
15 (1 AND 13) 8
16 (myalept).ti,ab 5
17 (mettreleptin).ti,ab 0
18 ("leptin A100").ti,ab 0
19 ("recombinant human leptin").ti,ab 161
20 exp "RECOMBINANT LEPTIN"/ 849
21 (16 OR 19 OR 20) 949
22 (10 AND 21) 87
23 ("leptin therap*").ti,ab 130
24 (10 AND 23) 31
25 1 [DT 2007-2017] [Languages English] 42

12 Evidence Selection

A total of 16 unique publications were initially identified following a library search based on the PICO document. Screening of abstracts resulted in 9 of these being selected for full text review.

An additional 13 unique publications were found via a search of narrative review citations. Screening of abstracts resulted in 7 of these publications being included for full text review. Also, a broad search for metreleptin yielded another 38 abstracts, of which 9 were found to have already been identified previously. Only 1 of these was selected for full text review after titles and abstracts were screened.

In total, 17 publications were selected for full text review. Of these, 7 papers were selected to be included as part of the evidence review and 1 non-systematic review paper was selected to be included within the narrative of the evidence review, without requiring evidence synthesis.

13 References

13.1 Literature Search Papers

Paz-Filho, G., Babikian, T., Asarnow, R., Esposito, K., Erol, H. K., Wong, M.-L. and Licinio, J. (2008a) 'Leptin Replacement Improves Cognitive Development', PLOS ONE, vol. 3, no. 8, p. e3098 [Online]. DOI: 10.1371/journal.pone.0003098.

Paz-Filho, G., Esposito, K., Hurwitz, B., Sharma, A., Dong, C., Andreev, V., Delibasi, T., Erol, H., Ayala, A., Wong, M.-L. and Licinio, J. (2008b) 'Changes in insulin sensitivity during leptin replacement therapy in leptin-deficient patients', American Journal of Physiology - Endocrinology and Metabolism, vol. 295, no. 6, pp. E1401–E1408 [Online]. DOI: 10.1152/ajpendo.90450.2008.

Paz-Filho, G., Mastronardi, C., Delibasi, T., Wong, M.-L. and Licinio, J. (2010) 'Congenital leptin deficiency: diagnosis and effects of leptin replacement therapy', Arquivos brasileiros de endocrinologia e metabologia, vol. 54, no. 8, pp. 690–697.

von Schnurbein, J., Moss, A., Nagel, S. A., Muehleder, H., Debatin, K. M., Farooqi, I. S. and Wabitsch, M. (2012) 'Leptin substitution results in the induction of menstrual cycles in an adolescent with leptin deficiency and hypogonadotropic hypogonadism', Hormone Research in Paediatrics, vol. 77, no. 2, pp. 127–133 [Online]. DOI: 10.1159/000336003.

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14 Appendices

14.1 Appendix 1: Study Participant Overlap

Table 2: Detail of participant overlap across the included studies

<table>
<tr><th>Paz-Filho et al., 2008a</th><th>Paz-Filho et al., 2008b*</th><th>Paz-Filho et al., 2010</th><th>von Schnurbein et al., 2012</th><th>von Schnurbein et al., 2013</th><th>Wabitsch et al., 2015a</th><th>Wabitsch et al., 2015b</th></tr>
<tr><td rowspan="2">7-year-old male born to a highly consanguineous Turkish family (parents are first-degree cousins).</td><td colspan="2" rowspan="2">Three leptin-deficient adults from a highly consanguineous Turkish family.</td><td colspan="2" rowspan="2">14-year-old, female first child of two healthy, non-obese Austrians without known consanguinity.</td><td rowspan="2">2 German siblings, (9-year-old girl and 6-year-old boy delivered to normal weight, caucasian parents without known consanguinity.</td><td rowspan="2">9 month old male born to two healthy, normal-weight Turkish parents with known consanguinity (first-degree cousins).</td></tr>
<tr><td>+1 child of Turkish Origin</td></tr>
</table>

*Paper ultimately excluded from the review due to significant overlap with Paz-Filho et al., 2010 as discussed in section 5