

## Could recombinant human leptin (metreleptin) be a new hope in the treatment of anorexia nervosa?

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Dear Editor,

Anorexia nervosa (AN) is the most lethal psychiatric disorder, mostly affecting young women. There is no treatment based on etiology. According to the results of recent studies, AN is now considered a metabo-psychiatric disease (Dmitrzak-Weglarz et al., 2016). Because studies have drawn attention to the biological changes in the brain associated with AN. Somatic and psychological symptoms of hunger are evident in AN. These symptoms are controlled by the weight loss-induced decline in circulating leptin levels. In humans, low-dose leptin administration has been reported to reverse the weight loss effects of energy expenditure and circulating thyroid hormones. Leptin levels in AN are below the normal range and slowly return to normal during weight gain. Hypoleptinemia-induced neuroendocrine adaptation involves up- or down-regulation of the hypothalamic-pituitary-gonadal, -thyroid, -adrenal, and -growth hormone axes. Leptin receptors located in various areas of the brain and the periphery are more sensitive to hunger. Because the primary symptoms of AN overlap with hunger symptoms, it has been suggested that treatment with human recombinant leptin (metreleptin) may reduce symptom burden and weight loss in AN. Studies with metreleptin have demonstrated significant improvements in mood, sleep, food preoccupation, internal tension, and hyperactivity in patients with AN. Metreleptin was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of the very rare lipodystrophy (Hebebrand et al., 2024). Recent case reports on seven patients diagnosed with AN suggest that off-label administration of metreleptin can result in profound and rapid relief of the complex symptomatology of AN. In light of the availability of only case reports, metreleptin is rated as low evidence with a weak recommendation for use in AN in the 2023 update guideline of the World Federation of Biological Psychiatry Associations on the pharmacological treatment of eating disorders. Leptin levels are often below 2 ng/mL in patients with AN. In addition to leptin secretion, the amount of soluble leptin receptors in circulation is very important for the free leptin index. The number of receptors is also increased in patients with AN. When weight gain begins, the low leptin levels slowly increase. For example, a case report study reported

a leptin level of 4 ng/mL after 80 days of inpatient treatment, with an increase in body mass index (BMI) of approximately 3 kg/m<sup>2</sup> in BMI of 12.7 kg/m<sup>2</sup> (Hebebrand et al., 2024). Metreleptin may potentially lead to rapid structural changes in brain regions such as the amygdala that are important for the psychopathology of AN (Wronski et al., 2023). In a recent study, the thalamic nucleus volumes of women diagnosed with AN were compared with the healthy group and most thalamic nucleus volumes were found to be reduced in patients with AN. It was stated that this reduction was positively correlated with leptin levels (Wronski et al., 2025). Thalamic nuclei change to different degrees in AN and laterodorsal nuclei appear to be significantly reduced. Leptin is implicated in the volume reduction of thalamic nuclei. These results seem to further support the investigation of experimental leptin treatment for AN. In a psychiatric interview conducted 14 and 165 days after starting metreleptin treatment in a 39-year-old female with congenital leptin deficiency to describe psychological changes, the most obvious initial experience was reduced preoccupation with food and improved mental health. These results are consistent with findings in patients with AN treated with metreleptin for 1–3 weeks. This case report provides important evidence that metreleptin has potent psychopharmacological effects in patients with absolute or relative leptin deficiency (Hebebrand et al., 2022). In another recent case report, a 17-year-old male adolescent with possible onset of myalgic encephalomyelitis after an Epstein Barr Virus infection (EBV) infection and subsequent onset of AN during a second period of weight loss was treated with metreleptin twice for 15 and 11 days, respectively. Metreleptin was administered subcutaneously at 9:00 AM for 15 days at doses of 3 to 6 mg/day, and his BMI at discharge was 18.8 kg/m<sup>2</sup>, compared with a baseline of 12.45 kg/m<sup>2</sup> (Hebebrand et al., 2023a). Another study evaluated the role of hypoleptinemia in irregular sleep by focusing on patients diagnosed with AN and stated that metreleptin may be useful in the treatment of treatment-resistant sleep-wake disorders associated with hypoleptinemia (Hebebrand et al., 2023b).

In conclusion, randomized controlled trials are clearly needed to confirm that metreleptin has profound effects on AN psychopathology and to examine whether it increases weight gain

with its possible contribution to treatment. Could metreleptin be a new hope in AN, where absolute or relative hypoleptinemia traps treatment resistance, leaving clinicians helpless?. Clinical trials are urgently needed to confirm that leptin analogs can reduce symptom burden and weight loss.

**Ethical Considerations:** Does this study include human subjects? NO.

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