Neuropsychopharmacology (2005) 30, 1770–1771

www.neuropsychopharmacology.org

Reply to Monteleone *et al*

Reply: Plasma Leptin and Antipsychotic-Induced Body Weight Gain

Dan Haupt*[,1] and John Newcomer[1]

[1]*Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA*

Neuropsychopharmacology (2005) **30,** 1770–1771. doi:10.1038/sj.npp.1300793

Sir

We appreciate the comments of Dr Monteleone and colleagues and share their interest in the hypothesis that variations in leptin signaling early in the course of antipsychotic treatment could contribute to variance in weight gain observed during treatment. They mention their own previously published study that detected a significant inverse correlation between plasma leptin early in the course of treatment and subsequent weight change, with higher leptin levels associated with lower weight increases (Monteleone *et al*, 2002). However, neither their study nor the studies cited in their paper included the control group necessary to test the implicit hypothesis mentioned above.

By way of background, individuals are hypothesized to experience a counter-regulatory increase in plasma leptin during weight gain, based on the established role of leptin as a satiety signal in rodents (Schwartz *et al*, 2000). The missing studies that we mention in our paper, which have not been reported to date, would address the question of whether leptin signaling during antipsychotic-induced weight gain is appropriate for the level of adiposity achieved by treated individuals. It is likely that many people experience counter-regulatory plasma leptin increases during weight gain that serve to discourage further weight gain. To test the hypothesis that antipsychotic weight gain is secondary to abnormal leptin secretion or signaling, one could perform a study consisting of prospective randomized assignment to an antipsychotic drug treatment expected to produce weight gain, to a negative control condition (placebo or antipsychotic not associated with weight gain), and, most importantly, to a positive control condition such as excess feeding with no change in medication. The comparison of interest would be between the two conditions where weight increased, in order to evaluate whether leptin signaling (eg crudely measurable *in vivo* in humans via plasma leptin) is over- or underelevated as compared to plasma leptin elevations seen during weight gain due to simple increase in caloric intake. If plasma leptin was underelevated compared to excess feeding, this might suggest that antipsychotic treatment may interfere with leptin secretion or clearance, in either case interrupting normal leptin signaling that might otherwise reduce treatment-associated weight gain. With sufficient sample size, one could further evaluate whether individual differences in plasma leptin during antipsychotic-induced weight gain could help to explain which subjects experience more or less weight gain. Previous reports have not offered either the important control conditions or sufficient sample size to appropriately test these questions.

Unfortunately, all these suggested studies would be time consuming and expensive to conduct. Given our inability to detect inappropriate plasma leptin levels in antipsychotic-treated patients in comparison to adiposity-matched controls, the case for undertaking these subsequent studies is weakened (Haupt *et al*, 2005). As stated in our paper, along with the recent report by Herran *et al*, evidence does not currently support the hypothesis that leptin regulation in schizophrenia patients during antipsychotic treatment, as compared to leptin regulation in untreated healthy controls, is due to impaired leptin secretion or leptin resistance (Haupt *et al*, 2005; Herran *et al*, 2001).

*Correspondence: Dr D Haupt, Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Avenue, Box 8134, St Louis, MO 63110, USA, Tel: +1 314 362 2592, Fax: +1 314 362 2025, E-mail: Hauptd@wustl.com
Received 5 April 2005; revised 22 April 2005; accepted 5 May 2005
Online publication: 5 May 2005 at http://www.acnp.org/citations/Npp042105040605/default.pdf

ACKNOWLEDGEMENTS

Drs Haupt and Newcomer have no significant financial conflicts of interest as defined by the Washington University School of Medicine Conflict of Interest Policy or this journal. Dr Haupt has received grant funding in the last year from NIMH, NARSAD, and Abbott Laboratories. Dr Newcomer has received grant funding in the last year from NIMH, NARSAD, the Sidney R Baer Foundation, Bristol-Myers Squibb, Janssen, and Pfizer.

REFERENCES

Haupt DW, Luber A, Maeda J, Melson AK, Schweiger JA, Newcomer JW *et al* (2005). Plasma leptin and adiposity during antipsychotic treatment of schizophrenia. *Neuropsychopharmacology* **30**: 184–191.

Herran A, Garcia-Unzueta MT, Amado JA, de La Maza MT, Alvarez C, Vazquez-Barquero JL *et al* (2001). Effects of long-term treatment with antipsychotics on serum leptin levels. *Br J Psychiatry* **179**: 59–62.

Monteleone P, Fabrazzo M, Tortorella A, La Pia S, Maj M (2002). Pronounced early increase in circulating leptin predicts a lower weight gain during clozapine treatment. *J Clin Psychopharmacol* **22**: 424–426.

Schwartz MW, Woods SC, Porte DJ, Seeley RJ, Baskin DG (2000). Central nervous system control of food intake. *Nature* **404**: 661–671.