

# Are Leptin and Cytokines Involved in Body Weight Gain During Treatment With Antipsychotic Drugs?

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**Objective:** To critically review published literature on the causal association between leptin, cytokines, and excessive body weight gain (BWG) induced by antipsychotic drugs (APs).

**Methods:** We completed a Medline search using the words leptin, cytokines, antipsychotic drugs, neuroleptics, psychotropic drugs, weight gain, and obesity. We also included our empirical research on this topic in the discussion. We examined the relation between leptin, cytokines (mainly tumour necrosis factor alpha [TNF- $\alpha$ ] and its soluble receptors), and AP-induced BWG, using the biological sciences' current theories of causality.

**Results:** In the general field of weight regulation, there is scarce experimental evidence that leptin or TNF- $\alpha$  by themselves can induce obesity. Serum levels of leptin and TNF- $\alpha$  rather increase simultaneously as BWG occurs. This has also been reported during AP-induced BWG, with the equivocal exception of a study with clozapine. Some researchers have suggested that the absence of the expected correlation between leptin and body mass index (BMI) or serum insulin levels, and the lack of sex-related differences in leptin levels in AP-treated patients, may point to a causal relation. This contention requires more experimental support. In addition, future clinical studies must carefully control for sex and BMI.

**Conclusions:** No conclusive evidence has been provided that leptin or TNF- $\alpha$  may induce obesity either in drug-free subjects or in AP-treated patients. In most cases, the elevated serum levels of these hormones appear to be a consequence rather than a cause of obesity. That does not mean that such an elevation is innocuous, since it may impair blood pressure and also carbohydrate and lipid metabolism regulation. Hence, all efforts should be made to prevent or attenuate BWG during treatment with APs.

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## Clinical Implications

- Elevated serum levels of leptin and TNF- $\alpha$  are physiologically expected in antipsychotic (AP)-treated patients who gain body weight. Most evidence suggests that such an elevation is a consequence and not a cause of excessive body weight gain (BWG).
- When high serum leptin levels are observed in AP-treated subjects with normal or low body mass index, it may be an important indicator of metabolic dysfunction, such as hyperinsulinemia and insulin resistance.
- Since leptin and TNF- $\alpha$  are involved in the development and maintenance of myocardial infarction, hypertension, and insulin resistance, excessive BWG during AP treatment must be prevented or lessened.

## Limitations

- The proposal that leptin and cytokines may induce excessive BWG during AP treatment has not received unequivocal experimental support.
- Clinical studies reporting anomalies in the expected correlation between leptin and relevant physiological variables or in the time-course of leptin or TNF- $\alpha$  elevation have important methodological limitations that preclude definitive conclusions.

**Key Words:** antipsychotic drugs, cytokines, insulin, leptin, obesity, weight regulation

Excessive body weight gain (BWG) induced by antipsychotic drugs (APs) was reported soon after the introduction of chlorpromazine in psychiatry (1). However, interest in this problem increased after 1990 because of the strong propensity of some new atypical agents to induce BWG (2–4). Multiple mechanisms are probably involved in AP-induced BWG, and most research has focused on AP effects on brain histamine, serotonin, dopamine, and central and peripheral acetylcholine, as well as on the metabolic-endocrine effects of hyperprolactinemia (1,5).

Pollmächer and others (6) and Melkersson and others (7,8), have suggested a relation between AP-induced BWG and cytokines (mainly tumour necrosis factor alpha [TNF- $\alpha$ ]) and leptin. Authorities in the field now frequently mention this relation (4,9), and the implicit assumption is that leptin or TNF- $\alpha$  may cause excessive BWG.

In this paper, we review the evidence relating leptin and TNF- $\alpha$  to AP-induced BWG. We first describe the main findings on leptin and TNF- $\alpha$  activity in cases of primary obesity. Second, we examine the studies that associate leptin and TNF- $\alpha$  to AP-induced obesity. Our discussion is based on the current theories of causality in chronic diseases.

### Leptin, TNF- $\alpha$ , and Primary Obesity

Leptin is a protein synthesized in the adipose tissue and, in minor proportions, in the placenta, stomach, and muscles (10). A few people and rodents lack leptin receptors in key tissues or display very low leptin production, along with severe obesity and diverse endocrine-metabolic abnormalities (11,12). Administration of the peptide to obese rodents lacking leptin decreases body weight (BW) and restores fertility (13). Leptin administration also decreases BW in obese or nonobese mice and rats (14,15) and in people with obesity not related to a leptin deficiency (16). In most humans and rodents, leptin serum levels correlate positively with body mass index (BMI: weight [kg] / height [m<sup>2</sup>]), with percentage of body fat, and with basal serum insulin levels (17,18). As an example, subjects with obesity or anorexia nervosa (AN) display higher and lower serum leptin levels, respectively, than do people with a normal weight. Importantly, these high or low leptin levels tend to normalize when an adequate BW is reached (19). Leptin levels are also higher in women than in men, even after correction for BMI (20).

Leptin is believed to be a messenger from the adipose tissue that signals the brain about the extent of body fat through a negative feedback regulatory mechanism. In turn, the nervous and endocrine systems should trigger a cascade of reactions to correct the increment or decrement in adipose tissue (11,12). However, an immediate question arises in relation to this model: Why don't the increased leptin levels in obese patients

correct excessive BW? It has been proposed that obesity is accompanied by a "leptin resistance" (10), a concept analogous to the insulin resistance observed in patients with diabetes and obesity. Such leptin resistance may be related to a decreased transport of the peptide through the blood-brain barrier and to postreceptor abnormalities (10).

TNF- $\alpha$  is a protein of the cytokine family. It is mainly synthesized by adipocytes and macrophages, but there is also local synthesis in the brain. It plays a prominent role in the mechanisms of tissue growth, inflammation, and immunity (6,21), and it is also involved in BW regulation. Intracerebral or systemic injections of TNF- $\alpha$  decreased food intake and BW in rodents (22). In addition, severe BW loss and anorexia were observed in mice transfected with the human TNF- $\alpha$  gene (23). In the adipocyte, TNF- $\alpha$  stimulates thermogenesis and lipolysis and decreases lipogenesis. Thus, it collectively decreases body fat and protein mass (21). In the cachectic states accompanying diverse diseases, TNF- $\alpha$  is massively synthesized in the macrophages and is one of the main factors mediating the severe anorexia observed in these conditions. Interestingly, high circulating TNF- $\alpha$  levels are found in obese subjects and correlate positively with the BMI and insulin and leptin levels (24). Converging evidence demonstrates that TNF- $\alpha$  impairs insulin sensitivity and is a critical factor in the insulin resistance and diabetes mellitus associated with obesity (25).

Argiles and others developed a model for TNF- $\alpha$  in BW regulation that resembles in some ways that of leptin (21). According to these authors, TNF- $\alpha$  functions in healthy subjects as an adipostat and assists the brain in preventing excessive fluctuations in BW. Hence, during cachexia, the activity of TNF- $\alpha$  is abnormally increased, whereas in obesity its action may be impaired (21).

Data obtained in some animal experiments suggest that TNF- $\alpha$  may promote BWG (26,27), since nonobese male mice with a targeted disruption of this cytokine gene (TNF- $\alpha^{-/-}$ ) displayed less weight than their intact control littermates (TNF- $\alpha^{+/+}$ ) (27). In addition, when the 2 groups of animals were exposed to a high-fat diet that induces obesity, the fat pads in the TNF- $\alpha^{+/+}$  group weighed significantly more than in the TNF- $\alpha^{-/-}$  group. As well, the BWG was nonsignificantly higher in the TNF- $\alpha^{+/+}$  group (26). However, using another model of obesity in mice (that is, the obese-obese model) and targeted mutations in 2 receptors for TNF- $\alpha$ , these authors found no difference in BWG and body composition between the obese mice with, or without, the receptor mutation (26). In a third model of obesity (induced by goldthioglucose, which causes chemical ablation of the ventromedial hypothalamus and induces hyperphagic obesity), a similar degree of obesity was obtained in TNF- $\alpha^{+/+}$  and TNF- $\alpha^{-/-}$

subjects (27). As a whole, these results show that TNF- $\alpha$  is not necessary to observe obesity in mice, even though the cytokine modulates BW in nonobese mice.

Collectively, these data suggest that leptin and TNF- $\alpha$  are hormones normally involved in physiological mechanisms regulating BW. However, once obesity is established, both hormones display deleterious effects on glucose homeostasis, blood pressure, and immunity.

Regarding the relation between leptin and the pathological regulation of BW, investigators are particularly attentive in describing subjects with abnormal or atypical correlations between leptin and the physiological variables that are relevant for BW regulation. It is thus of considerable scientific interest to find people in whom serum leptin levels do not correlate positively with BMI, with percentage of body fat, and with basal insulin levels or in whom changes in BW do not induce the expected changes in leptin levels. For example, subjects with hyperthyroidism or bulimia display lower leptin levels than would be expected for their BMI (28,29).

The initial conceptualization of the role of leptin in human physiology has evolved. It is now acknowledged that the peptide may be involved in numerous regulatory systems close or distal to signalling the body-fat size, such as the systems regulating nutrient availability, reproduction, hematopoiesis, the immune system, and the function of the adrenal and thyroid axis, among others (10). Initially, it also seemed implicit that the elevated leptin levels observed in cases of obesity were innocuous. This assumption has also been challenged, and converging evidence points to a role for leptin in the development of myocardial infarction (30), hypertension (31), insulin resistance (10), and prostatic cancer (32).

### Causality in Chronic Diseases

In obesity, as in many chronic diseases, the causal relations between the postulated factors and the pathological consequences are seldom linear and simple. Hill summarized 9 postulates in the complex field of causation that may assist researchers with the essential process of distinguishing between “association” and “causation” in human health and disease (33). The 9 postulates are strength, consistency, specificity, biological gradient, plausibility, coherence, experimental support, analogy, and temporality. In more recent reviews, the criterion of temporality (that is, the cause precedes the effect) often includes complex relations between the events such as simultaneity and circularity (34). Let us examine, as an example, how insulin (one of the most studied factors in obesity) fulfills the criteria of causality.

Most people with primary or secondary obesity display hyperinsulinemia (which satisfies the criteria of strength and consistency). Chronic hyperinsulinemia generally leads to

obesity (which meets the criterion of specificity). The extent of hyperinsulinemia (and other components of the metabolic syndrome, such as dyslipidemia, hypertension, and insulin resistance) increases as the BMI progresses, reaching a plateau around BMI 34 (35). In addition, BWG in insulin-treated rats is dosage-dependent (meeting the criteria of biological gradient and experimental support) (36). The metabolic effects of insulin promote BWG since it enhances lipogenesis, gluconeogenesis, and protein synthesis (37). Hence, it may be deduced that hyperinsulinemia induces obesity (meeting the criteria of plausibility, coherence, and analogy). In relation to the criterion of temporality, there are clear examples where hyperinsulinemia precedes BWG. These include insulinomas in humans, administration of exogenous insulin (36), and the high serum insulin levels quickly observed in rats after lesions of the ventromedial hypothalamus (38).

Unfortunately, this simple scheme of causality for insulin in obesity is further complicated by at least 2 important facts. First, insulin decreases appetite by acting in the brain, and this action is opposite to its peripheral effects on metabolism (12). Second, other factors are involved in primary obesity, such as abnormalities in appetite, in resting metabolic rate, in energy cost of activity, in fat oxidation, and in leptin and insulin sensitivity. Because of this, hyperinsulinemia develops simultaneously with BWG (39).

Let us briefly review the evidence for the role of leptin and TNF- $\alpha$  as factors that induce obesity. Both hormones are elevated in obese people, and their serum levels correlate with BMI and insulin levels (fulfilling the criteria of strength, consistency, and biological gradient). Yet, TNF- $\alpha$  levels are also increased in cachexia (21), and high leptin levels may be observed in normal-weight subjects (7). Hence, the criterion of specificity is not fulfilled. Most experimental evidence described above suggests that leptin and TNF- $\alpha$  decrease appetite and BW. No published study has reported BWG or obesity directly induced by any of the hormones (displaying a lack of experimental support). Perhaps researchers are prone to make an analogy between leptin, TNF- $\alpha$ , and insulin, thus meeting the criteria for plausibility and coherence, but more empirical support is needed. We speculate that studies showing leptin and TNF- $\alpha$  to impair insulin sensitivity may have led researchers to suspect that these hormones may also impair the mechanisms of BW regulation (and hence cause or aggravate obesity). This is plausible; however, such deleterious effects generally seem to be induced after BWG has already occurred. Thus, more empirical data are needed to sustain the contention.

This leads us to the important criteria of temporality. Few experimental studies have shown high leptin levels before actual BWG. A remarkable example but one difficult to extrapolate

in the daily clinical arena is the hyperleptinemia detected in rats immediately after an experimentally induced lesion of the ventromedial hypothalamus, followed by a progressive BWG and subsequent obesity (38). In fact, Ravussin and others showed that low serum leptin levels predicted subsequent BWG in Pima Indians, a population at high risk for obesity and diabetes (39).

Regarding TNF- $\alpha$ , Hinze-Selch and others showed that, in clozapine-treated subjects, the effects on sTNFRp75 (a soluble receptor of the hormone) preceded the increase in the BMI (40). Hence, they conclude: "Our data suggest that weight gain may be a consequence of an induction of the TNF- $\alpha$  system" (40, p 17). We discuss this study in detail later, but to conclude this section, we emphasize that most studies have shown that leptin and TNF- $\alpha$  increase simultaneously with BW. It seems then, that both BWG and high hormone levels are triggered by a suprafactor (for example, increased appetite, low levels of resting metabolic rate, energy cost of activity, fat oxidation, or high insulin sensitivity) (41).

### **Do leptin or TNF- $\alpha$ induce BWG in humans or animals treated with APs?**

We conducted a Medline search using the words leptin, cytokines, antipsychotic drugs, neuroleptics, psychotropic drugs, weight gain, and obesity. We found 11 articles dealing directly with the topic of AP-induced BWG. In this section, we briefly review the reports in which leptin or TNF- $\alpha$  were assessed during treatment with APs. As previously discussed, some authors suggested a causal relation between leptin or TNF- $\alpha$  and AP-induced BWG, based on anomalies in the expected correlation between these hormones and some physiological variables. Our main arguments are that these studies were not primarily designed to establish causality and that the postulated anomalies warrant replication after improvement in some relevant methodological issues. For the benefit of interested readers, we present a detailed description of some papers, their main results, and the proposed anomalies observed in some studies (Table 1).

### **What do these results tell us about causality between leptin or cytokines and AP-induced BWG?**

Before discussing the above-indicated articles, we will summarize the type of results (and the anomalies) that might be expected to support a causal link between leptin and cytokines and excessive BWG. Experimental studies should demonstrate that exogenous administration of these hormones induces obesity in animals. High serum levels of the hormones should be observed before obesity has developed, and blocking the effects of leptin and TNF- $\alpha$  might prevent BWG. An

important variation could be that the hormones might further impair the mechanisms of BW regulation once obesity is established, which would make it difficult to return to a normal BW. The anomalous findings could be the lack of correlation between the basal hormone levels and insulin, BMI, BWG, and appetite. The expected sex-related difference for leptin (that is, higher levels in women) might also be lost.

In the following paragraphs we critically discuss the above-mentioned reports, with regard to causality. It will be apparent that criteria for a causal relation between leptin, TNF- $\alpha$ , and AP-induced BWG have not yet been fulfilled.

All the human studies reported a significant increase in leptin and BW during AP treatment (7,8,40,42–48). A serum leptin increase (by fat accumulation) is expected during BWG in most people. Hence, the criterion of specificity is not fulfilled. No leptin increase was observed in studies wherein BW was not significantly affected during administration of haloperidol (43), sulpiride (44), or lithium (49). In an early experimental study, we reported that rats with sulpiride-induced obesity had leptin levels similar to those of vehicle-treated animals (50). We recently demonstrated the same lack of leptin elevation in risperidone-treated rats, in spite of significant BWG (unpublished research). In both cases, the difference in BWG between AP-treated rats and control animals was small, though statistically significant. However, a different experimental protocol that induced robust BWG in sulpiride-treated rats indeed showed a significant increase in serum leptin levels. It thus appears that, in contrast to humans (44), the magnitude (threshold) of BWG necessary to observe significant changes in leptin levels is higher in genetically intact rats.

Melkerson reported that the expected correlation between leptin levels, BMI, and insulin was absent and that olanzapine-treated women did not display significantly higher leptin levels than did olanzapine-treated men (7,8). These interesting findings seem to show an abnormal or anomalous leptin regulation during olanzapine administration and are implicitly used by the authors to support a causal relation between leptin and AP-induced BWG. However, in our prior review of the Melkerson and others study (51), we commented that 2 methodological limitations precluded any firm conclusion: first, the lack of pretreatment values for leptin and insulin and, second, the presence of 2 subjects with very abnormal leptin and insulin levels, despite normal BMI (see Table 1). In fact, when the data were reanalyzed excluding these patients, the expected correlation between leptin, BMI, and insulin was actually observed. Nonetheless, in a response to our letter, Melkerson and Hulting argued that there were no reasons to exclude these subjects.

Regarding the lack of sex differences in leptin levels (8), we also suggested that, ideally, this study should have been

Authors	Treatment	Results	Anomalies
Melkerson and others (7) and Melkerson and Hulting (8)	Conventional APs ( $n = 19$ ) clozapine ( $n = 14$ ) olanzapine ( $n = 14$ )	Leptin levels increased after olanzapine administration	In olanzapine-treated patients, the expected correlation between leptin, insulin, and BMI was absent.  The normally observed sex difference in leptin levels (higher in women) was found in the conventional AP group, but not in the clozapine or olanzapine groups.
Hinze-Selch and others (40)	Clozapine ( $n = 12$ ) and clozapine + fluvoxamine ( $n = 11$ )	The increase in plasma leptin levels was significantly stronger and faster during the combined therapy.  The BWG was similar in both treatment groups.	The observed elevation in leptin levels during the combined therapy cannot be explained by the changes in BW.
Bromel and others (42)	Clozapine ( $n = 12$ )	Serum leptin levels and BW significantly increased.	None
Kraus and others (43)	Clozapine ( $n = 11$ ) olanzapine ( $n = 8$ ) or haloperidol ( $n = 13$ )	Leptin levels significantly increased in patients who gained BW during clozapine or olanzapine administration. During haloperidol administration, no changes were observed in BW or in leptin levels.	None
Baptista and others (44)	Sulpiride in healthy volunteers: 12 women and 7 men	In men, BW and leptin levels significantly increased. In women, neither BW nor leptin were significantly affected.	None
Baptista and others (45)	A combination of typical APs (haloperidol, fluphenazine, chlorpromazine) in psychotic women and a group of age- and BMI-matched healthy volunteers	Leptin levels did not differ in the 2 groups. Obese subjects (patients and controls) displayed higher leptin levels than those with normal BMI.	None
Herran and others (46)	Conventional depot APs ( $n = 17$ ); conventional oral APs ( $n = 26$ ); risperidone ( $n = 5$ ); clozapine ( $n = 5$ ); olanzapine ( $n = 7$ ). Control group: healthy subjects matched by sex, age and BMI	Leptin levels did not differ between patients and control subjects in the whole sample.  In patients with atypical APs, leptin levels were significantly higher in the olanzapine group, intermediate in the clozapine group, and lower in the risperidone group ( $P = 0.03$ ).	Clozapine-treated patients displayed lower leptin levels than expected for their BMI.  Olanzapine appears to induce a greater increase in leptin, independently of BWG.
Eder and others (47)	Olanzapine	A significant increase in BW, leptin levels, and percentage of body fat was observed during olanzapine administration.	None
Hagg and others (48)	Clozapine ( $n = 41$ ) conventional APs ( $n = 62$ ) healthy control subjects ( $n = 189$ )	After adjustment for sex, BMI, and other variables, hyperleptinemia was independently associated with treatment with clozapine ( $P < 0.001$ ) or conventional APs ( $P < 0.001$ ).	In women, leptin levels were not significantly associated with treatment with conventional APs.

AP = anti[psychotic]; BW = body weight; BMI = Body Mass Index; BWG = Body weight gain; TNF- $\alpha$  = tumor necrosis factor- $\alpha$

conducted by strictly pairing men and women by BMI, age, and ethnic group. We think this should be considered in future comparisons between olanzapine and other APs, since the positive correlation between BMI and leptin is one of the strongest and most consistent findings in the field. In fact, Baptista and others showed that women with obesity associated with typical AP-administration had leptin levels similar to healthy control subjects matched by age, BMI, and day of the menstrual cycle (45). This result seems to prove that observed elevated leptin levels are not specific to subjects who gain BW during AP administration.

Similarly, we commented elsewhere (52) that the anomalies observed by Herran and others (47) are inconclusive because the sample was too small ( $n = 5$ ), and the subject's sex was not specified in the report. Herran and others reported that clozapine-treated patients displayed lower leptin levels than expected for their BMI; however, an overrepresentation of men in the clozapine group (or women in the olanzapine group) may explain their results, since women display higher leptin levels than do men after controlling for BMI. Herran and others' claim that "olanzapine appeared to induce a greater increase in leptin independently of weight gain" is

very important, since again, it points to an olanzapine-related deleterious metabolic profile. Unfortunately again, these results are inconclusive because of the small sample size ( $n = 7$ ) and the absence of data directly comparing the olanzapine-treated subjects and matched control subjects.

Melkerson and Hulting speculate that clozapine and olanzapine may induce leptin resistance at the hypothalamic level and thus impair the ability of leptin to properly regulate BW (8, p 210). This is an interesting suggestion; however, there are no published empirical data on this topic. In addition, leptin resistance appears to be a general trait in primary obesity (11). It is thus unclear how leptin resistance could be a specific effect of the above-mentioned APs. In any event, if this is confirmed, it would rather support the contention that leptin prevents rather than promotes AP-induced BWG.

In their study of patients treated with clozapine alone or clozapine plus fluvoxamine, Hinze-Selch and others reported the anomaly that the observed results in leptin levels cannot be explained by the changes in BW (40). Specifically, the increase in the leptin plasma levels was significantly stronger and faster in patients on combined therapy, even though the data on BW and BMI did not follow the same pattern. However, a detailed evaluation of their Table 5 shows that the rate of BW change was different in the 2 groups. Subjects in the combined treatment group gained 1.2 kg in the first 2 weeks, whereas the net change during that period for subjects receiving clozapine alone was 0 kg. (In fact, the clozapine group lost 0.9 kg in the first week). This is reflected in the leptin levels: the net change in the first 2 weeks was 10 and 2.1 ng/ml for the combined and monotherapy groups, respectively. For the combined and monotherapy groups, the net BW change for the whole 6 weeks of treatment was 5 and 3.3 kg, respectively; the net leptin-level change was 10.6 and 3.9 ng/ml, respectively. When assessed in isolation, the changes in both variables appear congruent and proportional. However, in the between-group comparisons, only leptin achieved statistical significance. The authors emphasize that finding to further support the postulated dissociation between leptin and BW. Still, it may be argued that the difference in total BW gain (1.7 kg), while statistically nonsignificant, may be physiologically relevant for leptin regulation. In fact, we found that, after a BW gain of just 0.61 kg, leptin levels doubled in healthy men treated with the AP sulpiride (44). Lastly, we wonder whether a different statistical analysis might have produced other results—for example, if leptin levels had been analyzed separately in patients who gained BW and those who did not or if the data had been analyzed by paired comparisons within the same subjects (that is, before-and-after tests). This appears particularly relevant when the high variability in leptin levels is considered.

Results obtained with the cytokines are difficult to interpret in regard to BW regulation. In this study, TNF- $\alpha$  and soluble interleukin-2 receptor (sIL-2r) levels were significantly higher in the monotherapy group (receiving clozapine alone), which tended to gain less BW. This finding, in isolation, allows speculation that those cytokines rather prevented or

lessened the drug effects on BW. The soluble cytokine receptors (sTNFRp55 and sTNFRp75) significantly increased within each group, but the between-group comparisons were nonsignificant. However, in another study of 10 olanzapine-treated patients (in which 7 were observed to gain weight significantly), the same authors reported no changes in IL-6, sIL-2r and TNF- $\alpha$  levels (53), although sTNFRp55 and sTNFRp75 did increase significantly. In their paper, Schuld and others did not intend to reconcile their findings with olanzapine with those obtained by their research group in a study with clozapine: TNF- $\alpha$ , sIL-2r, sTNFRp55, and sTNFRp75 levels and BW significantly increased during clozapine monotherapy (40), but only sTNFRp55 and sTNFRp75 increased (along with BW) during olanzapine treatment. Thus, we are left with the difficult suggestion (not stated by the authors) that TNF- $\alpha$  and sIL-2r may induce BWG in clozapine-treated, but not in olanzapine-treated, subjects. This is of course possible, but few data appear to support it. Again, we wonder what might be the results if cytokines were compared between subjects who gained BW and those who did not.

To reconcile several disparate findings about the role of TNF- $\alpha$  in BW regulation, Basile and others (9) adhere to the proposal that this cytokine may display anabolic effects, and hence it may promote obesity, when it displays physiological increase. Conversely, when TNF- levels are elevated at supra-physiological levels, this cytokine may rather display catabolic effects and thus promote BW loss, as in cachexia. Basile and others further speculate that this hypothesis may explain an interesting observation: the higher the BMI before starting AP treatment, the smaller the amount of BWG (for example, during olanzapine administration [54]). A problem remains, however: the catabolic effects of TNF- $\alpha$  appear to be observed in people whose BMI is higher than 45. This is an extreme degree of obesity that may exclude a patient from clinical trials. In fact, only 10 out of 186 subjects had a BMI > 40 in an olanzapine study (Lilly, personal communication, 2002). Hence, most patients with high basal BMI (> 27.6) were well below the threshold value of 45 and still gained little BW. In any case, this interesting proposal deserves further investigation.

In another recent study, Basile and others reported that patients who had an A/A genotype for the G-308A polymorphism of the TNF- $\alpha$  gene and displayed high cytokine levels reported more BWG during clozapine administration than did patients with other genotypes (and lower TNF- $\alpha$  levels) (9). This important result supports the notion that TNF- $\alpha$  may promote obesity in AP-treated patients. As discussed above, however, and given the many contradictory findings in this field, future studies must address the alternative explanation that such high TNF- $\alpha$  levels may represent a compensatory response to prevent additional BWG in predisposed organisms.

Finally, the anomaly reported by Hagg and others—lack of association between treatment with conventional APs and high leptin levels—may be explained by a lack of power in the

linear regression model used, as stated by the authors (48). Hagg and others speculate that interaction between conventional APs and androgens might contribute to the observed sex differences, since leptin levels correlate directly to testosterone levels in healthy nonobese women. Thus, abnormal androgen levels should be detected in women after long-term treatment with typical APs. However, this prediction was not confirmed in a recent study (45).

## General Conclusions

Primary obesity and AP-induced obesity are complex chronic diseases, and few factors (except increased appetite and food consumption) have been definitively shown to cause those conditions. Leptin and TNF- $\alpha$  are critically involved in BW regulation. Most scientific evidence suggests that the high serum levels of both hormones observed in obese people are consequences rather than causes of the disease. However, they impair insulin sensitivity, which in turn promotes glucose intolerance and cardiovascular diseases. It is plausible that leptin and TNF- $\alpha$  further impair BW regulation and indirectly perpetuate obesity. Currently, however, this assertion is only a matter of speculation. More experimental studies exploring the effects of leptin and cytokines on BW regulation during AP treatment are required. Finally, clinical studies on this topic must carefully control for relevant variables such as sex and BMI.

## Implications of Elevated Leptin and TNF- $\alpha$ Serum Levels in Patients With AP-Induced Obesity

At present, the most parsimonious conclusion is that the increased serum levels in leptin and TNF- $\alpha$  in these patients is mainly a direct consequence of BWG and not a specific phenomenon related to AP treatment. Interestingly, however, the Melkerson and others study (7) offers the possibility that some olanzapine-treated patients particularly sensitive to drug-induced metabolic dysregulation may display high leptin and insulin levels despite having normal BW. This may be related to insulin resistance, which prevents BWG and promotes serum glucose increase. Hence, this leptin-BW dissociation might be observed in patients receiving other APs.

Further studies should assess whether such hormone elevation further impairs the mechanisms of weight regulation. Converging evidence points to the role of these cytokines in the development and maintenance of myocardial infarction (30), hypertension (31), insulin resistance (10), and prostatic cancer (32). Therefore, excessive BWG and obesity must be prevented or lessened in the general population and in AP-treated patients.

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**Résumé : La leptine et les cytokines participent-elles à la prise de poids durant le traitement aux antipsychotiques?**

**Objectif :** Procéder à l’analyse critique de la documentation publiée sur l’association causale entre la leptine, les cytokines et la prise de poids (PP) excessive entraînée par les antipsychotiques (AP).

**Méthodes :** Nous avons effectué une recherche dans Medline à l’aide des mots leptine, cytokines, antipsychotiques, neuroleptiques, psychotropes, prise de poids et obésité. Nous avons également inclus notre recherche empirique à ce sujet dans la discussion. Nous avons examiné la relation entre la leptine, les cytokines (surtout le facteur onconécrosant- $\alpha$  [TNF- $\alpha$ ] et ses récepteurs solubles), et la prise de poids entraînée par les AP, à l’aide des théories de causalité actuelles des sciences biologiques.

**Résultats :** Dans le domaine général de la régulation du poids, il existe peu de preuves expérimentales que la leptine ou le TNF- $\alpha$  à eux seuls peuvent causer l’obésité. Les taux sériques de leptine et de TNF- $\alpha$  s’accroissent plutôt simultanément à la prise de poids. C’est aussi ce qui a été déclaré durant une prise de poids induite par les AP, à l’exception ambiguë d’une étude sur la clozapine. Des chercheurs ont suggéré que l’absence de corrélation prévue entre la leptine et l’indice de masse corporelle (IMC) et le manque de différences selon le sexe des taux de leptine chez les patients traités aux AP peuvent indiquer une relation causale. Cette hypothèse nécessite plus de soutien expérimental. En outre, les futures études cliniques doivent contrôler soigneusement le sexe et l’IMC.

**Conclusions :** Aucune preuve concluante n’a été fournie que la leptine ou le TNF- $\alpha$  peuvent entraîner l’obésité tant chez les sujets non médicamenteux que chez les patients traités aux AP. Dans la plupart des cas, les taux sériques élevés de ces hormones semblent être une conséquence plutôt qu’une cause de l’obésité. Cela ne veut pas dire que cette augmentation est inoffensive, puisqu’elle peut entraver la tension artérielle ainsi que la régulation du métabolisme des glucides et des lipides. Ainsi, il faut tout tenter pour prévenir ou atténuer la prise de poids durant le traitement aux AP.