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Meta-analysis of ghrelin alterations in schizophrenia: Effects of olanzapine

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ABSTRACT

Objective: Schizophrenia is associated with an increased prevalence of the metabolic syndrome. Patients receiving antipsychotic medications, including olanzapine, are at further risk. Ghrelin is an appetite-stimulating peptide hormone, although whether blood levels are altered by antipsychotic treatment, remains unclear. We performed a systematic review and meta-analysis comparing blood ghrelin levels in patients with schizophrenia before and after treatment with olanzapine.

Method: Two authors independently searched major electronic databases from inception until February 2018 for studies measuring blood ghrelin levels among patients with schizophrenia before and after olanzapine therapy. Random effects meta-analysis calculating standardized mean difference (SMD) and 95% confidence intervals (CI) and meta-regression analyses were performed.

Results: Six studies met the inclusion criteria. Across these studies, there were 111 patients with schizophrenia (mean age 40, 85% male, baseline BMI 22, and endpoint BMI 23). Olanzapine treatment (mean [standard deviation] duration = 12.3 [7.6] weeks) was associated with a significant decrease in blood ghrelin levels with a medium effect size (SMD = −0.48, 95% CI −0.88 to −0.08, $p = 0.018$). Age, sex, baseline BMI, geography, olanzapine dose and duration, year of publication, study quality, inpatient status, and antipsychotic washout did not moderate this association.

Conclusion: Our results suggest that in patients with schizophrenia, olanzapine therapy is associated with decreased blood ghrelin levels, a paradoxical phenomenon known to occur in obesity. Future studies should investigate the contribution of dietary factors (e.g., caloric intake) and physical activity to this association, as well as the effects of other antipsychotics on ghrelin levels.

1. Introduction

The metabolic syndrome is a constellation of metabolic risk factors associated with the development of type 2 diabetes mellitus, atherosclerotic cardiovascular disease, and all-cause mortality (Kaur, 2014). Patients with schizophrenia have an increased prevalence of the metabolic syndrome, with the highest risk found in patients treated with clozapine or olanzapine (Vancampfort et al., 2015). Second generation antipsychotics like olanzapine have been noted to induce weight gain, a major contributing factor to the development of metabolic syndrome (Rege, 2008), which may be driven by increased caloric intake (Fountaine et al., 2010). Type 2 diabetes is also highly prevalent in patients with schizophrenia, with a higher risk in antipsychotic-treated patients (Vancampfort et al., 2016). The increased prevalence of metabolic syndrome and diabetes contributes to the dramatically increased risk of premature mortality in patients with schizophrenia compared to the general population (Hayes et al., 2017; Walker et al., 2015). However, the mechanism(s) of antipsychotic-associated weight gain are complex and multifactorial. The role of several endogenous peptides—including leptin, ghrelin, and orexins—in antipsychotic-associated weight gain has been investigated. A recent meta-analysis of 27 studies found that schizophrenia is associated with increased blood leptin levels, with a small effect size, compared to controls (Stubbs et al., 2016).

Ghrelin is a 28 amino acid peptide produced primarily in the stomach, but also the hypothalamus, with a stimulatory effect on appetite and the secretion of growth hormone (GH) at the level of the hypothalamus (Takaya et al., 2000). Ghrelin functions by stimulating the synthesis of neuropeptide Y (NPY) and Agouti-related protein (AgRP) by neurons in the arcuate nucleus, which in turn stimulate production of orexins in the lateral hypothalamic area, resulting in increased appetite and food intake via the vagus nerve (Chen et al., 2004; Gropp et al., 2005; Guan et al., 1997; Kamegai et al., 2001). Injections of exogenous ghrelin increase appetite more than any other substance (besides

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neuropeptide Y), and lead to increased body weight (Asakawa et al., 2001; Wren et al., 2001). Total circulating ghrelin includes two forms with differential effects: des-acyl ghrelin (>90%) and acyl ghrelin (<10%). Ghrelin becomes active via acylation at the serine 3 position with an n-octanoic acid group (Gil-Campos et al., 2006). The acyl group of ghrelin is essential for receptor binding and associated appetite stimulation. Des-acyl ghrelin, which is a structurally similar molecule that acts as a functional inhibitor of ghrelin and can suppress ghrelin levels. Des-acyl ghrelin can decrease appetite and food intake (Gil-Campos et al., 2006).

There is substantial between-study heterogeneity regarding the literature on blood ghrelin levels in schizophrenia. Cross-sectional studies have reported both significantly increased (Basoglu et al., 2010; Esen-Danaci et al., 2008) and significantly decreased (Lu et al., 2015; Togo et al., 2004) blood ghrelin levels in patients with schizophrenia compared to controls. Several factors may contribute to discordant findings, including phase of illness (e.g., first-episode versus chronic schizophrenia), assay methodology (e.g., total versus active ghrelin), medication status of the patients (i.e., treated versus untreated), and differential effects of various antipsychotic medications. Meta-analysis is one approach that can bring increased clarity to an area of research with significant heterogeneity (Sullivan et al., 2003), and thus is well suited to the study of blood ghrelin levels in schizophrenia. As an important next step, in order to investigate the effects of antipsychotic medication on these associations, we performed a systematic review and meta-analysis of the change blood ghrelin levels in patients with schizophrenia after treatment with olanzapine.

2. Methods

2.1. Study selection

This systematic review was conducted in accordance with the MOOSE guidelines (Stroup et al., 2000) and in line with the PRISMA statement (Moher et al., 2009). A copy of the MOOSE checklist is available as Supplementary material. Studies of the effect of olanzapine on ghrelin levels in schizophrenia were identified by a systematic search using Medline (PubMed, National Center for Biotechnology Information, US National Library of Medicine, Bethesda, Maryland) and Thomson Reuters (formerly ISI), PsycInfo (via Ovid, American Psychological Association, Washington, DC), Web of Science (Science Citation Index and Social Sciences Citation Index, Thomson Reuters, Charlottesville, Virginia) in February 2018. The primary search strategy was: "(ghrelin AND "schizophrenia OR psychosis")", limiting results to studies with abstracts in English. The initial search yielded 136 articles. After the removal of duplicates, 91 articles were screened. We also manually reviewed the reference lists of these screened articles for potentially relevant studies that did not appear in any of the database searches. The majority of the initial matches were excluded because they were review articles, did not present data on ghrelin, were animal studies, or were genetic studies related to ghrelin polymorphisms or receptors.

We included longitudinal studies that measured ghrelin levels in patients with schizophrenia before and after treatment with olanzapine. Ideally, we would have performed meta-analyses of both cross-sectional and longitudinal studies of ghrelin levels in patients with schizophrenia. However, we note that relevant cross-sectional studies had significant heterogeneity with regards to treatment status (i.e., treated versus untreated patients) and assay methodology (i.e., total versus active ghrelin). There were not an adequate number of studies to perform a cross-sectional meta-analysis of untreated patients with schizophrenia versus controls. Furthermore, given the variable metabolic effects across different second-generation antipsychotics (Rummel-Kluge et al., 2010), there were not adequate studies to perform either cross-sectional or longitudinal meta-analyses of ghrelin levels in patients treated with specific antipsychotics, except for longitudinal studies of olanzapine. The exclusion criteria were: 1) studies without longitudinal data (e.g., case-control studies), 2) studies that did not present either mean and standard deviations (SDs) or median and interquartile range (IQR) for ghrelin levels (after attempting to contact the study authors – two separate emails to at least two different study authors), 3) significant overlap in study population, and 4) genetic studies related to ghrelin polymorphisms or receptors.

After independent searches, review of study methods and reference lists by both authors (RLG and BJM) and attempts to contact other authors, 6 studies met the inclusion/exclusion criteria, (Basoglu et al., 2010; Hosojima, 2005; Kim et al., 2008; Smith et al., 2012; Stip et al., 2012; Tanaka et al., 2008;). There was universal agreement on the included studies. A flow chart summarizing the study selection process is presented in Fig. 1.

2.2. Study quality assessment

Both authors (RLG and BJM) independently assessed study methodological quality. A standardized checklist was used, modified from other checklists of longitudinal studies (Kuijpers et al., 2004) and based on methodological and theoretical considerations (Altman, 2001). The checklist contained 11 criteria scored as either being present (1 point) or absent (0 points), for a maximum score of 11. Checklist items covered aspects of validity and generalizability. A copy of the checklist items and study scoring is included in Supplementary material.

2.3. Data extraction and meta-analysis

Data were extracted (sample size, mean/SD or median/IQR for patients), for ghrelin assessed in each study. If necessary, we estimated the mean/SD from the median/IQR using the following formulas: (1) mean = (2 m + a + b)/4, where m is the median and a and b are the 25th and 75th percentiles, respectively (Hernandez et al., 2014) and (2) IQR = 1.35 × SD (Higgins and Deeks, 2011). One author (RLG) extracted all data, which was independently verified by another author (BJM). We then calculated effect size ES estimates (Standardized Mean Difference [SMD]) for the difference in ghrelin levels for each study, and these data are included in Supplementary material. Random effects pooled ES estimates and 95% confidence intervals (95% CIs) were calculated using the method of DerSimonian and Laird for patients with schizophrenia before and after olanzapine therapy. *p*-Values were considered statistically significant at $\alpha = 0.05$ level. The statistical analyses were performed in Stata 10.0 (StataCorp LP, College Station, TX).

The meta-analysis procedure also calculates a χ^2 value for the heterogeneity in ES estimates, which is based on Cochran's Q-statistic (Cochran, 1950), and I^2, the proportion of the variation in ES attributable to between-study heterogeneity. χ^2 was considered significant for $p < 0.10$ (Song et al., 2001), in which case we performed a sensitivity analysis. This was done by removing one study at a time and repeating the meta-analysis procedure, to examine its impact on the SMD and between-study heterogeneity (Higgins and Green, 2011).

We also performed a series of meta-regressions for ghrelin levels in schizophrenia to explore possible moderating variables of age, sex, baseline BMI, geography, dose and duration of olanzapine treatment, year of publication, study quality score, inpatient status (yes/no), and antipsychotic washout (yes/no). We were not able to perform meta-regression analyses for other possible moderating variables (e.g., illness duration and smoking) due to the absence of adequate data. Potential for publication bias was examined with Sterne's funnel plot analysis (Sterne and Egger, 2001) and Egger's regression intercept (Egger et al., 1997).

3. Results

3.1. Study and participant characteristics

Table 1 presents details of the included studies. Across the 6 longitudinal studies, there were 111 patients with schizophrenia (mean age 40,

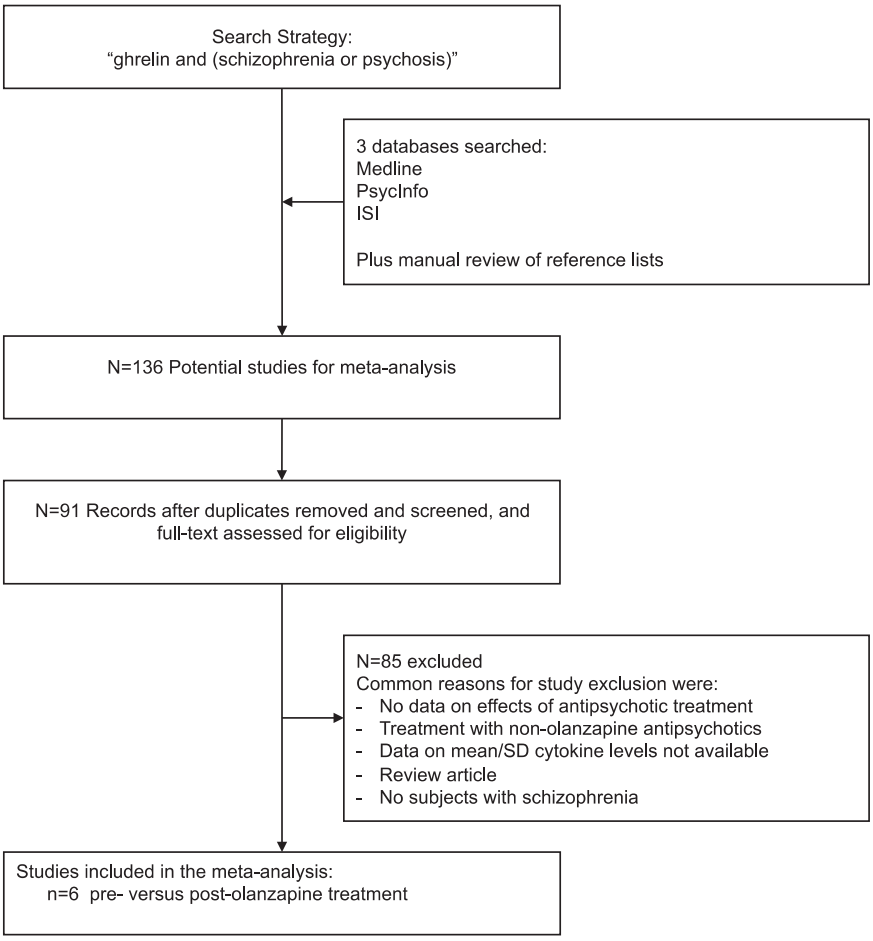


Fig. 1. Flow chart of the study selection process.

85% male, baseline BMI 21.7, and endpoint BMI 22.7). The mean (SD) dose and duration of olanzapine treatment was 18.0 (4.6) mg (range 12–25) and 12.3 (7.6) weeks (range 4–24 weeks), respectively. Mean study quality score was 8.3 (range 6–11). Four of the six studies were performed on inpatients. A different set of four of the studies had an antipsychotic washout period of at least 2 weeks.

Table 1
Longitudinal studies of ghrelin and olanzapine treatment in schizophrenia.

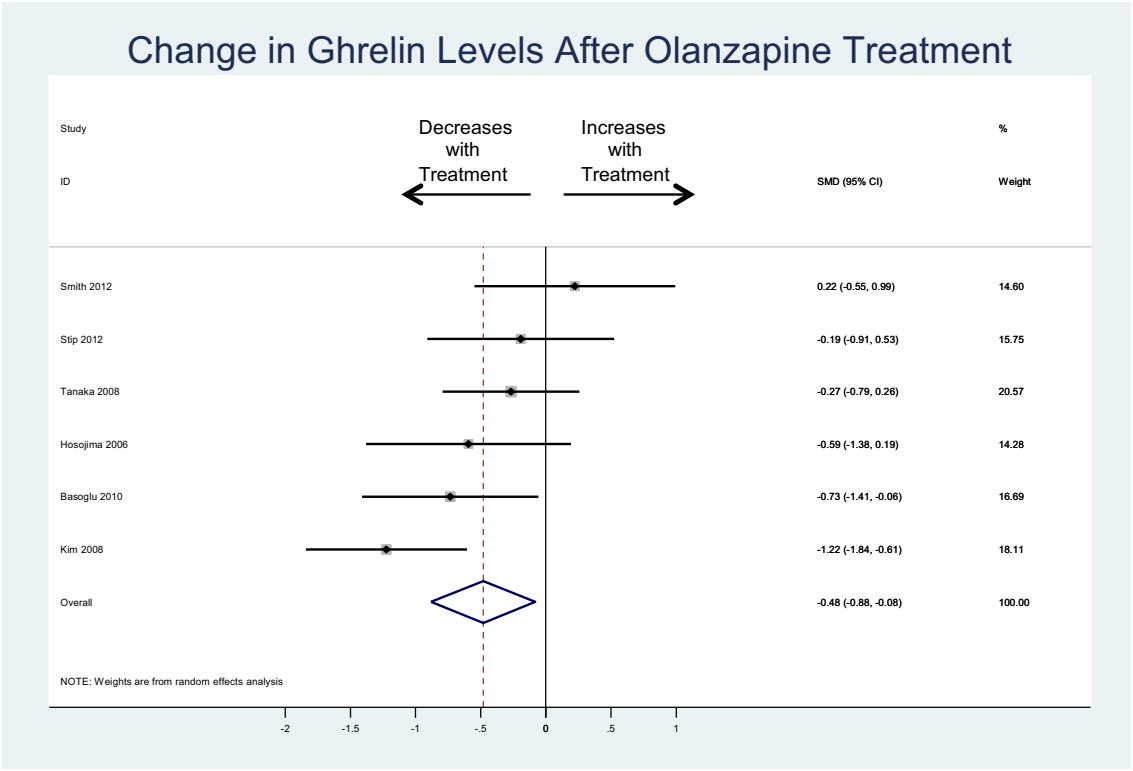
Study	Location	Assay	Marker	Time of assay	Fasting	N	Mean age	% male	Mean baseline BMI	Mean endpoint BMI	Mean dose (mg)	Trial length (weeks)	Quality score	Treatment details
Stip et al., 2012	Canada	RIA	Total ghrelin	Morning	Yes	15	35.8	73	N/A	N/A	16	16	6	Outpatients; No history of olanzapine exposure; Switched to olanzapine due to insufficient response to other antipsychotics; No washout
Basoglu et al., 2010	Turkey	ELISA	Total ghrelin	7 am	Yes	18	21.2	100	22.4	24.4	20	6	9	Inpatients with first-episode, antipsychotic-naïve psychosis
Hosojima, 2005	Japan	RIA	Active ghrelin	8–10 am	Yes	13	37.0	86	20.3	20.9	15	4	7	2/3 outpatients, 1/3 inpatients No antipsychotic exposure in past 4 weeks
Tanaka et al., 2008	Japan	RIA	Total ghrelin	7 am	Yes	28	59.5	64	22.2	22.2	20	16	10	Inpatients; Switched to olanzapine from either risperidone or typical antipsychotics; 2 week washout period
Kim et al., 2008	S. Korea	RIA	Total ghrelin	7–8 am	Yes	24	34.3	100	21.3	23.1	12	24	11	Inpatients; 2 week washout period
Smith et al., 2012	U.S.	RIA	Total ghrelin	Morning	Yes	13	41.2	98	N/A	N/A	25	8	7	Inpatients; Switched from another antipsychotic; No washout

N/A = not available.
ELISA = enzyme-linked immunosorbent assay.
RIA = radioimmunoassay.

3.2. Meta-analysis of change in ghrelin levels with olanzapine treatment in schizophrenia

Olanzapine treatment was associated with a significant decrease in blood ghrelin levels with a medium effect size (SMD = −0.48, 95% CI −0.88 to −0.08, $p = 0.018$) and significant between-study heterogeneity (heterogeneity $\chi^2 = 10.60$, $p = 0.06$, $I^2 = 52.8\%$ Fig. 2a). In a sensitivity analysis, after excluding one outlying study (Smith et al., 2012), the effect size remained significant (SMD = −0.60, 95% CI −0.98 to −0.28, $p = 0.002$) and between-study heterogeneity was no longer significant (heterogeneity $\chi^2 = 6.83$, $p = 0.15$, $I^2 = 41.4\%$). In another sensitivity analysis including one study that measured active (versus total) ghrelin, the effect size remained significant (SMD = −0.48, 95% CI −0.77 to −0.19, $p = 0.00$), with significant between-study

a. Forest plot of meta-analysis.



b. Funnel plot of meta-analysis

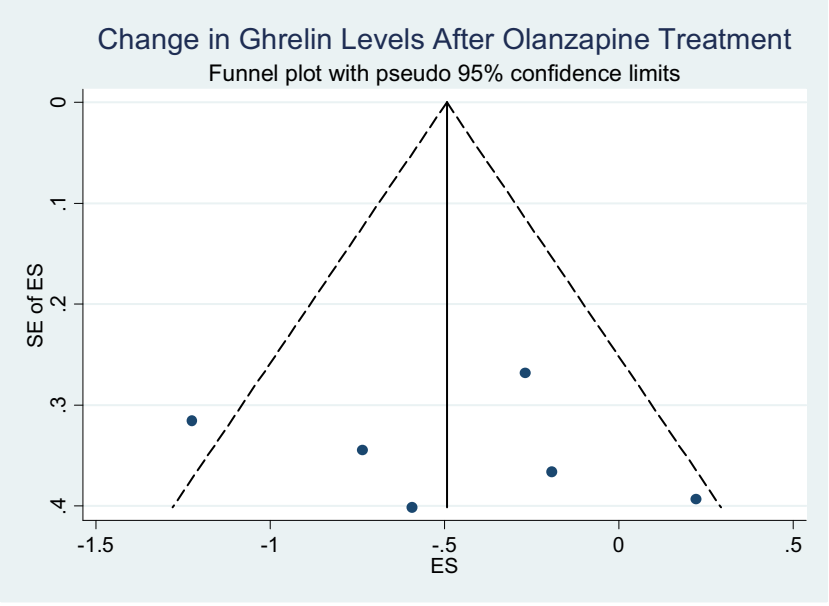


Fig. 2. Meta-analysis of changes in blood ghrelin levels with olanzapine treatment in schizophrenia.

heterogeneity (heterogeneity $\chi^2 = 10.51$, $p = 0.03$, $I^2 = 62.0\%$). There was no evidence of publication bias (Egger's test $p = 0.72$; funnel plot included in Fig. 2b). In meta-regression analyses, age, sex, baseline BMI, geography, olanzapine dose and duration, year of publication, study quality score, inpatient status, and antipsychotic washout did not moderate the association between ghrelin and olanzapine treatment ($p > 0.05$ for each).

4. Discussion

To our knowledge, ours is the first meta-analysis of blood ghrelin levels in patients with schizophrenia. We found that olanzapine treatment (mean dose 18 mg, range 12–25) was associated with a significant decrease in ghrelin levels, over a mean of 12.3 weeks (range 4–24), in these patients with a medium effect size. This association was not moderated by age, sex, baseline BMI, geography, study quality, year of publication, dose or duration of treatment, inpatient status, or antipsychotic washout.

The strengths of our study include the pooled sample size, the availability of longitudinal data, and the investigation of potential moderating factors in meta-regression analyses. There are always limitations to studies. We did not perform a meta-analysis of blood ghrelin levels in patients with schizophrenia versus controls. There were an insufficient number of studies of to perform meta-analyses of 1) patients with first-episode/antipsychotic-naïve schizophrenia versus controls, and 2) antipsychotic-free patients with chronic schizophrenia versus controls. Future studies in these patient populations would be important to understanding the specific effects of illness (schizophrenia) on the association with blood ghrelin levels. We observed significant between-study heterogeneity regarding the association between blood ghrelin levels and treatment with olanzapine, although this heterogeneity was no longer significant in a sensitivity analysis removing one outlying study (Smith et al., 2012). Data were not available to investigate other potential confounding or moderating factors such as smoking, socioeconomic status, and dietary factors (e.g., caloric intake), and physical activity/sedentary behavior, which may have impacted on the internal validity of findings. Future studies should investigate these parameters. We were also unable to perform a meta-analysis of the effects of other, non-olanzapine, antipsychotics on blood ghrelin levels in patients with schizophrenia due to an insufficient number of studies, which affects the external validity of our findings.

The finding that early olanzapine therapy is associated with decreased blood ghrelin levels seems, at first, paradoxical. Olanzapine, a medication known to cause increased appetite and weight gain, reduces the level of an appetite-stimulating hormone. However, ghrelin levels are known to fall in obesity. The exact mechanism of this is not clearly understood; however, it may be related to increased leptin and insulin levels in these patients (Tschöp et al., 2001). This pattern is broadly consistent with previous meta-analytical data, which found significantly increased leptin levels (effect size = 0.40) in patients with schizophrenia receiving second generation antipsychotics (Stubbs et al., 2016), as well as increased insulin levels and insulin resistance in antipsychotic-naïve patients with non-affective psychosis (Greenhalgh et al., 2017).

A randomized, double-blind, placebo-controlled trial with a crossover design in lean, healthy males found that olanzapine-induced weight gain via increased caloric intake, which may be attributable to serotonin 5-HT2c receptor antagonism (Fountaine et al., 2010). This raises the possibility that the observed changes in ghrelin with olanzapine treatment are secondary to weight gain/obesity. It is imperative that future studies of ghrelin in schizophrenia assess and control for dietary factors and physical activity/sedentary behavior. It would also be informative to investigate the effects of treatment with other non-olanzapine antipsychotics on ghrelin levels, to evaluate the specificity of this association.

An 8-week study of olanzapine treatment in rodents found a non-significant decrease in blood ghrelin levels (Horska et al., 2016). A previous qualitative review in schizophrenia found that fasting morning ghrelin levels briefly decrease with the initiation of atypical antipsychotic treatment, but are increased with continued treatment (Sentissi et al., 2008). We found quantitative evidence for decreased ghrelin levels following olanzapine therapy, however our findings do not preclude the possibility of increased ghrelin with longer-term antipsychotic treatment. The mean and median length of olanzapine therapy in the present meta-analysis was 12 weeks (i.e., relatively short duration), and only one study measured changes in ghrelin over a period longer than 16 weeks. Therefore, additional studies of longer duration are needed to better understand the long-term effects of olanzapine on ghrelin levels. It would also be informative to measure ghrelin levels weekly for the first 4–8 weeks of antipsychotic treatment, towards a clearer picture of the early effects of olanzapine therapy.

Ghrelin-induced modulation of stress has been linked to alterations in hypothalamic-pituitary-adrenal HPA axis and autonomic nervous system function, as well as serotonergic neurotransmission (Bali and Jaggi, 2016). Antipsychotic-induced hyperphagia and weight gain are associated with hypothalamic ghrelin signaling in animal models (Zhang et al., 2014). Concordantly, BMI-corrected ghrelin levels predicted higher disinhibition subscale scores on the Three-Factor Eating Questionnaire in patients with schizophrenia compared to healthy controls (Schanze et al., 2008). Genetic factors are also relevant to the observed associations. The −604 G/A polymorphism in the ghrelin gene is associated with greater increased BMI following atypical antipsychotic treatment (Yang et al., 2012). Another study found that the rs696217 SNP for the *GHRL* gene (ghrelin and obestatin prepropeptide) was associated change in BMI and appetite during antipsychotic treatment in patients with schizophrenia (Ryu et al., 2016).

Our understanding of the pathophysiology of ghrelin in antipsychotic-associated obesity is complicated by is the concept of active ghrelin. Most of the early ghrelin assays measured total ghrelin, which is composed of both active and des-acyl ghrelin. The latter antagonizes the effects of active ghrelin, and therefore may have contributed to the heterogeneity observed in previous studies. This finding suggests that measuring active and des-acyl ghrelin separately may represent a more optimal approach to the study of ghrelin in patients with schizophrenia (Delhanty et al., 2012).

5. Conclusions

We found meta-analytic evidence that early olanzapine treatment is associated with a significant decrease in ghrelin levels in patients with schizophrenia. Understanding the pathophysiology of antipsychotic-associated metabolic risks is an important step in addressing the burden of cardiometabolic morbidity and mortality in this patient population. More longitudinal research is required to better understand differential effects of illness, medications, dietary factors and lifestyle choices on ghrelin levels, and their relationship to measures of both mental and physical health in patients with schizophrenia.

CRediT authorship contribution statement

Ryan L. Goetz: Conceptualization, Formal analysis, Supervision, Writing - review & editing. **Brian J. Miller:** Conceptualization, Formal analysis, Supervision, Writing - review & editing.

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None.

Conflict of interest

Mr. Goetz has nothing to disclose relevant to the present work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.11.036.

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