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REVIEW ARTICLE

Association between Serum Lipids and Antipsychotic Response in Schizophrenia

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Abstract: Metabolic abnormalities are serious health problems in individuals with schizophrenia. Paradoxically, studies have noted an association where individuals who gained body weight or who have increased their serum lipids demonstrated a better antipsychotic response. As serum lipids serve as more specific physiological markers than body weight, the objective of this study was to review studies that examined the association between changes in serum lipids and changes in symptoms during antipsychotic treatment in individuals with schizophrenia. A Medline® literature search was performed. Fourteen studies were included and analyzed. Evidence suggests that increases in serum lipids may be associated with decreases in symptoms during antipsychotic treatment. This inverse association may be independent of confounding variables, such as weight gain, and may be most evident during treatment with clozapine. Also, according to recent randomized controlled trials, lipid-lowering agents do not appear to worsen symptoms although this needs to be further investigated in clozapine-treated patients. Future studies should investigate the association in question in a larger population and identify underlying mechanisms.

Keywords: Serum lipids, triglycerides, cholesterol, dyslipidemia, antipsychotics, treatment response, clozapine, schizophrenia.

1. INTRODUCTION

Metabolic abnormalities are serious health problems among individuals with schizophrenia [1]. For instance, the estimated prevalence of obesity, dyslipidemia, and metabolic syndrome in schizophrenia is 45–55%, 25–69%, and 37–63%, respectively [1]. These metabolic abnormalities elevate the risk of cardiovascular disease, which is a leading cause of premature mortality among adults with schizophrenia in the United States with a standardized mortality ratio of 3.6 (95% confidence interval, 3.5-3.6) [2]. Studies show that lifestyle factors that increase the risk of metabolic abnormalities, such as poor dietary habits, low physical activity, sedentary behavior (*e.g.*, sitting or lying down), and smoking, are more prevalent in individuals with schizophrenia compared with the general population [1].

Antipsychotic treatment itself can be a risk factor and may further increase the risk of metabolic abnormalities in schizophrenia [3]. Second-generation antipsychotics (SGAs) are known to induce cardiovascular and metabolic side effects, including weight gain, dyslipidemia, and diabetes [3]. These effects are particularly associated with clozapine and olanzapine [3]. Proposed mechanisms underlying SGA-induced weight gain include antagonism of dopamine D_2, histamine H_1, and 5-HT_{2C} receptors [3]. Studies show that antipsychotic-induced dyslipidemia is independent of weight gain and can occur at an early stage of antipsychotic treatment before the presence of weight gain [4, 5], indicating that the two side effects may follow different mechanisms. However, exact mechanisms underlying antipsychotic-induced lipid disturbances are still not clear, although peripheral alterations of peroxisome proliferator-activated receptors and progesterone receptor membrane component 1/insulin-induced gene 2, and thus increased biosynthesis of lipids in the liver, may be involved [3, 5]. It should be noted that antipsychotic-naïve individuals with psychosis demonstrate subclinical dyslipidemia, which may be explained by unhealthy lifestyle factors [6].

Over the past decade, a number of studies have identified a paradoxical relationship between weight gain and clinical improvement during antipsychotic treatment [7]. That is, individuals with schizophrenia who gained more weight during antipsychotic treatment experienced greater improvements in their symptoms. Our group took a step further and investigated whether a more specific physiological marker than body weight (*i.e.*, serum lipids) might independently predict clinical improvement in individuals with schizophrenia during treatment with clozapine and/or risperidone [8]. We found that increase in serum total cholesterol (TC) and

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triglyceride (TG) levels were associated with decrease in total Positive and Negative Syndrome Scale (PANSS) scores and PANSS negative subscale scores, independent of changes in body weight [8]. Similarly, we reported a case in which a patient showing a good response to clozapine relapsed following a 7-week course of a lipid-lowering agent (*i.e*., atorvastatin) that significantly reduced his serum TC and TG concentrations [9, 10]. Upon discontinuation of atorvastatin, the patient's serum TC and TG concentrations increased, coinciding with a considerable improvement in his symptoms.

In this review, we aim to evaluate the association between changes in serum lipids and changes in symptoms during antipsychotic treatment in individuals with schizophrenia to determine the significance of serum lipids as potential predictors of antipsychotic response.

2. METHODS

A Medline® literature search was performed to identify studies that examined the association between levels of serum lipids and symptoms over the course of antipsychotic treatment in individuals with schizophrenia. The following combination of keywords or MeSH terms was used: ("lipid*" or "cholesterol" or "triglyceride*") and ("PANSS" or "BPRS" or "positive symptom/syndrome" or "negative symptom/syndrome") and ("correlat*" or "associat*" or "relation*") and ("schizo*" or "psychosis" or "Psychotic Disorders"). Reference sections of identified studies were screened for additional relevant studies. Only English language human publications were included. Studies had to meet the following inclusion criteria: 1) used any of the following serum lipid variables: TC, TG, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and very low-density lipoprotein cholesterol (VLDL-c), 2) used any of the following psychiatric rating scales: PANSS, Brief Psychiatric Rating Scale (BPRS), and Scale for the Assessment of Positive/Negative Symptoms, and 3) examined the relationship between the changes in serum lipid variables and changes in symptom variables over the course of antipsychotic treatment. Studies were excluded if they examined the relationship using a cross-sectional study design. This is because the objective of this review was to examine the association between serum lipids and symptoms during a given period of antipsychotic treatment to evaluate the significance of serum lipids as potential predictors of antipsychotic response. All titles and abstracts were read by D.D.K. The last search was conducted on June 26, 2018.

3. RESULTS

The Medline® search yielded 184 publications. Twenty studies investigated the relationship between serum lipids and symptoms in individuals with schizophrenia. Of these, 9 articles were excluded because they utilized a cross-sectional study design. The supplementary search through the reference sections of the identified studies resulted in the inclusion of two additional articles. Thus, a total of 14 studies that reported on the relationship between serum lipids and symptoms of schizophrenia over the course of antipsychotic treatment were retained [8, 9, 11-21]. One study was a case report, two were randomized controlled trials, and 11 were observational studies. Included studies are summarized in Table **1**.

Among the studies that reported the association between changes in serum lipids and changes in symptoms (n = 12) [8, 9, 11-16, 18, 19, 21, 22], 9 studies found inverse associations [8, 9, 11-13, 15, 16, 18, 21], whereas three studies did not find significant associations [14, 19, 22]. The remaining two studies found significant associations but carried out the analysis without using repeated measures of the dependent and independent variables. Specifically, one study investigated the association of a single (baseline) assessment of PANSS scores with changes in serum lipids [17], whereas the other study investigated the association of a single (baseline) measurement of serum lipid levels with a single (follow-up) assessment of PANSS scores [20]. As the results of these studies are difficult to interpret, the main focus of this review will be on the 12 studies that reported the association between changes in serum lipids and changes in symptoms over time [8, 9, 11-16, 18, 19, 21, 22].

3.1. A Case

The earliest study reporting an inverse association between serum lipids and symptoms was in 2002. Pande *et al*. (2002) reported a case in which a patient showing good response to clozapine (225 mg/d) relapsed following a 7-week course of a lipid-lowering agent (*i.e*., atorvastatin) that significantly reduced his serum TG and TC concentrations from 74.8 to 9.7 mmol/L and 15.4 to 5.4 mmol/L, respectively [9]. Upon discontinuation of atorvastatin, the patient's serum TG and TC concentrations increased after 5 weeks from 9.7 to 70.8 mmol/L and 5.4 to 19.1 mmol/L, respectively, coinciding with a considerable improvement in his symptoms.

3.2. Studies that Performed Simple Correlation Analyses

Garyfallos *et al*. (2003) examined the correlation between changes in serum lipid levels and changes in PANSS scores in 50 participants with schizophrenia spectrum disorders treated with olanzapine or risperidone over an 8-week period [11]. The authors found a significant correlation between increased serum TG levels and symptom improvement (*i.e*., reductions in PANSS total scores) in the olanzapine group ($r = 0.71$, $p < 0.001$), but not in the risperidone group. Atmaca *et al*. (2003) examined this relationship in 64 participants with schizophrenia treated with clozapine, olanzapine, or risperidone over a 12-month period [12]. The authors found a significant correlation between increased serum TG levels and symptom improvement (*i.e*., reductions in PANSS total scores) in the clozapine group ($r = 0.60$, $p < 0.05$) and in the olanzapine group ($r = 0.58$, $p < 0.05$), but not in the quetiapine or risperidone group.

3.3. Studies that Performed Linear Regression Analyses

Procyshyn *et al*. (2007) examined the relationship in 55 participants with treatment-resistant schizophrenia receiving clozapine monotherapy (51%) or a combination of clozapine and risperidone (49%) over an 8-week period [8]. After controlling for changes in body weight, every increase of 1 mmol/L in serum TG significantly predicted a decrease of

Table 1. Summary of studies on the relationship between serum lipids and symptoms of schizophrenia.

Publication, Country, Study Design	Demographics	Diagnosis	Antipsychotic Medication	Follow-up Duration	Serum Lipid Measures	Symptom Measures	Controlling for	Relationship between Serum Lipids and Symptoms
Pande *et al*., 2002 [9]; Canada; case study	N = 1 (26 yr; male)	SCZ	Clozapine	26 weeks	TC, TG	BPRS	N/A	1) Clozapine-associated increases in TC and TG coincided with symptom improvement. 2) Atorvastatin-associated decreases in TC and TG coincided with relapse. 3) Increases in TG and TC after atorvastatin discontinuation coincided with symptom improvement.
Garyfallos *et al*., 2003 [11]; Greece; prospective study	N = 50 (mean age range: 31.5 ± 6.1–31.8 ± 6.5 yr; 68% male)	SCZ spectrum disorders	Olanzapine or risperidone	8 weeks	TC, TG	PANSS	None	1) Significant inverse association of Δ TG with Δ PANSS total in olanzapine group (n = 25; r = 0.71, p < 0.001).* 2) No significant relationship in risperidone group (n = 25).
Atmaca *et al*., 2003 [12]; Turkey; prospective study	N = 64 (mean age range: 27.9 ± 7.8–32.1 ± 6.2 yr; 45% male)	SCZ	Clozapine, olanzapine, quetiapine, or risperidone	12 months	TG	PANSS	None	1) Significant inverse association of Δ TG with Δ PANSS total in clozapine (n = 14; r = 0.60, p < 0.05) and olanzapine (n = 14; r = 0.58, p < 0.05) groups.* 2) No significant relationship in quetiapine (n = 14) and risperidone (n = 14) groups.
Huang *et al*., 2005 [13]; Taiwan; prospective study	N = 97 (mean age: 32.3 ± 9.4 yr; 51% male)	SCZ	FGA: haloperidol, loxapine, or sulpiride; SGA: clozapine, olanzapine or risperidone	3 weeks	TC, TG, HDL-c, LDL-c, VLDL-c	PANSS (responder: ≥50% reduction in PANSS total score)	none	1) Responders to SGAs (n = 32): significant increases in TC, TG, HDL-c, VLDL-c. 2) Responders to FGAs (n = 36): no significant changes in lipid profiles. 3) Nonresponders (n = 29): no significant changes in lipid profiles.
Procyshyn *et al*., 2007 [8]; Canada; RCT	N = 55 (mean age: 37.06 ± 9.80 yr; 75% male)	SCZ	Clozapine + risperidone/placebo	8 weeks	TC, TG	PANSS (responder: ≥20% reduction in PANSS total score)	Δ body weight	1) Significant inverse association of Δ TC with Δ PANSS negative (B = -2.36, p = 0.007). 2) Significant inverse associations of Δ TG with Δ PANSS total (B = -3.74, p = 0.037) and negative (B = -1.57, p = 0.017). 3) Responders: significant increases in TC and TG compared with nonresponders.
Hermes *et al*., 2011 [14]; USA; prospective study	N = 865 (mean age: 40.6 ± 11.1 yr; 74% male)	SCZ	FGA: perphenazine; SGA: olanzapine, quetiapine, risperidone, or ziprasidone	3 months	TC, TG	PANSS	Baseline serum lipid and PANSS values, antipsychotic use, investigator site, age, duration of illness	No significant relationship between Δ serum lipids and Δ PANSS (data not reported).
Lally *et al*., 2013 [15]; UK, observational study	N = 49 (mean age: 37.4 ± 9.3 yr; 67% male)	SCZ	Clozapine	6 months	TC, TG, HDL-c, LDL-c	PANSS	Δ body weight, Δ waist circumference, Δ serum clozapine levels	Significant inverse association of Δ TG with Δ PANSS total (B = 9.33, p < 0.001), positive (B = 2.85, p = 0.001), and negative (B = 1.93, p = 0.02).*

(Table 1) contd….

Publication, Country, Study Design	Demographics	Diagnosis	Antipsychotic Medication	Follow-up Duration	Serum Lipid Measures	Symptom Measures	Controlling for	Relationship between Serum Lipids and Symptoms
Terevnikov *et al*., 2013 [16]; Finalnd; RCT	N = 36 (mean age range: 43.4–48.2 yr; 51% male)	SCZ	FGA (various) + mirtazapine/placebo	Weeks 0–6 (Phase I); Weeks 6–12 (Phase II)	TC	PANSS	Duration of illness, antipsychotic dose, Δ body weight, Δ fasting glucose	1) Significant inverse association of Δ TC (increase of 1 mmol/L) with Δ PANSS total (reduction of 7 points, p = 0.001), positive (reduction of 1.7 points, p = 0.03), negative (reduction of 1.8 points, p = 0.004) in FGA-mirtazapine group. 2) No significant relationship in FGA-placebo group (based on linear regression). 3) No significant relationship in either group in Phase II.
Chen *et al*., 2014 [17]; Taiwan	N = 372 (mean age: 49.2 ± 9.7 yr; 75% male)	SCZ	FGA/SGA	2 years	TC, TG, HDL-c, LDL-c	PANSS	Age, sex, antipsychotic use	1) Significant inverse associations of Δ TG with baseline PANSS total (Estimate = -0.60, p = 0.007) and PANSS negative (Estimate = -1.74, p < 0.001) 2) Significant positive association of Δ HDL-c with baseline PANSS negative (Estimate = 0.21, p = 0.004).
Sharma *et al*., 2014 [18]; India; prospective study	N = 100 (mean age range: 28.1 ± 7.07–31.3 ± 8.1 yr; 46% male)	SCZ spectrum disorders	SGA (≥ 82%): risperidone (65.3%), olanzapine (16.7%), other (18.1%)	2–4 weeks (first follow-up); 8–12 weeks (second follow-up)	TC, TG, HDL-c, LDL-c, VLDL-c	BPRS	Δ appetite	1) Significant inverse association of Δ TG with Δ BPRS at first follow-up (R^2 = 0.16, p = 0.001). 2) Significant inverse association of Δ TG at first follow-up with Δ BPRS at second follow-up (R^2 = 0.17, p = 0.009).
Chukhin *et al*., 2016 [19]; Finland; RCT	N = 35 (mean age: 37.3 ± 18.3 yr; 100% male)	97% SCZ	Clozapine/olanzapine with orlistat/placebo	16 weeks	TC, TG, HDL-c, LDL-c	PANSS	None	No significant relationship between Δ serum lipids and Δ PANSS in either orlistat (n = 18) or placebo (n = 17) group (data not reported).
Solberg *et al*., 2016 [20]; Norway; naturalistic study	N = 55 (mean age: 26.5 ± 6.1 yr; 69% male)	SCZ or SAD	Unmedicated, n = 11; FGA, n = 5; SGA, n = 39	5 years	TC, TG	PANSS	None	Significant positive association of baseline TG with follow-up PANSS total (r = 0.28, p = 0.04).
Gjerde *et al*., 2017 [21]; Norway; prospective study	N = 132 (mean age: 26.7 ± 7.6 yr; 64% male)	FEP	SGA (88%; various) with/without FGA (16%; various)	12 months	TC, TG, HDL-c, LDL-c	PANSS	Age, sex, antipsychotic use, BMI	Significant inverse association of Δ HDL-c with Δ PANSS negative (B = -0.54, p = 0.02).
Luckhoff *et al*., 2018 [22]; South Africa; longitudinal study	N = 106 (mean age: 24.2 yr; 73% male)	FEP	Flupenthixol decanoate (100%)	12 months	TC, TG, HDL-c, LDL-c	PANSS	Age, sex, ethnicity, substance use, antipsychotic dose, treatment duration, other co-medications	1) Significant inverse association of Δ TG with Δ disorganized symptoms (r = -0.29; p = 0.040). 2) Δ TG was not a significant predictor in a linear regression model.

Abbreviations: BMI: body mass index; **BPRS**: Brief Psychiatric Rating Scale; **FEP**: first-episode psychosis **FGA**: first-generation antipsychotic; **HDL-c**: high-density lipoprotein cholesterol; **LDL-c**: low-density lipoprotein cholesterol; **PANSS**: Positive and Negative Syndrome Scale; **SAD**: schizoaffective disorder; **SCZ**: schizophrenia; **SGA**: second-generation antipsychotic; **TC**: total cholesterol; **TG**: triglycerides; **VLDL-c**: very low-density lipoprotein cholesterol. *PANSS reduction was included in the analyses as clinical improvement.

3.74 points in PANSS total scores and 1.60 points in PANSS negative subscale scores [8]. Also, every increase of 1 mmol/L in serum TC significantly predicted a decrease of 2.36 points in PANSS negative subscale scores [8]. Lally *et al*. (2013) examined the relationship in 49 participants with schizophrenia receiving clozapine monotherapy over a 6-month period [15]. After controlling for changes in body weight, waist circumference, and serum clozapine levels, every increase of 1 mmol/L in serum TG levels significantly predicted a decrease of 9.33 points in PANSS total scores,

2.85 points in PANSS positive subscale scores, and 1.93 points in PANSS negative subscale scores [15]. Terevnikov *et al*. (2013) examined the relationship in participants with schizophrenia treated with first-generation antipsychotics (FGAs) augmented with mirtazapine (n = 20) or FGAs with placebo (n = 16) over a period of 6 weeks of double-blind treatment [16]. After controlling for duration of illness, antipsychotic dose, body weight change, and fasting glucose level change, every increase of 1 mmol/L in serum TC levels significantly predicted a decrease of 7.0 points in PANSS total scores, 1.7 points in PANSS positive subscale scores, and 1.8 points in PANSS negative subscale scores in the FGA-mirtazapine group, but no significant associations were observed in the FGA-placebo group [16]. Sharma *et al*. (2014) examined the relationship in 71 participants with schizophrenia spectrum disorders treated with a mix of antipsychotics [18]. After controlling for changes in appetite, increases in serum TG levels from baseline to the first follow-up (2–4 weeks) significantly predicted reductions in BPRS scores after the first follow-up ($R^2 = 0.16$; p = 0.001) and after the second follow-up (8–12 weeks; $R^2 = 0.17$; p = 0.009) [18]. Gjerde *et al*. (2018) examined the relationship in 132 participants with first-episode psychosis treated with a mix of antipsychotics over a period of 12 months [21]. After controlling for changes in body mass index (BMI), every increase of 1 mmol/L in serum HDL-c levels significantly predicted a decrease of 0.54 points in PANSS negative subscale scores [21].

3.4. Studies that Performed Responder/nonresponder Analyses

In addition to performing a hierarchical multiple regression analysis, Procyshyn *et al*. (2007) performed a Mann-Whitney U analysis on the rankings of changes in serum lipid concentrations for the responders versus the nonresponders treated with clozapine monotherapy or clozapine-risperidone polypharmacy [8]. Defining response as a 20% reduction in PANSS total scores at 8-week follow-up, the authors found that responders demonstrated significantly increased serum TG (+21% vs. -10%, $U = 126.0$, p = 0.004) and TC (+7% vs. -4%, $U = 139.5$, p = 0.008) concentrations versus non-responders [8]. Huang and Chen (2005) examined responders (defined as a reduction 50% in PANSS total scores at 3-week follow-up) versus nonresponders [13]. Similar to our study, responders to any treatment (FGA or SGA) showed a significant increase in serum TG (+23.6 mg/dL, p = 0.003) and TC (+7.0 mg/dL, p = 0.040) from baseline [13]. Stratifying the data further, participants that responded to SGAs demonstrated an even greater increase in serum TG (+34.3 mg/dL, p = 0.004) and TC (+11.8 mg/dL, p = 0.045) concentrations from baseline [13]. Interestingly, participants that responded to FGAs did not show any significant changes in lipid profile from baseline.

3.5. Studies that did not Find Significant Associations

Three studies did not find significant associations between changes in serum lipids and changes in symptoms in schizophrenia. Using the data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, Hermes *et al*. (2011) evaluated the relationship between changes in BMI as well as serum TC or TG levels with changes in symptoms in individuals with schizophrenia treated with perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone [13]. Although a statistically significant association between changes in BMI and changes in PANSS total scores was noted, neither serum TC nor TG levels had a significant association with changes in symptoms [13]. In a 16-week study that randomized patients treated with either clozapine or olanzapine to add-on orlistat or placebo, Chukhin *et al*. reported that there was no association of changes in BMI as well as serum TC or TG levels with changes in PANSS total scores [18]. Lastly, Luckhoff *et al*. (2018) performed a 12-month longitudinal study to investigate the association of weight gain and changes in other metabolic variables with symptom improvement in first-episode schizophrenia spectrum disorder patients treated with flupenthixol decanoate [21]. Both weight gain and increases in TG levels were inversely correlated with reductions in PANSS disorganized symptoms, but only weight gain was a significant predictor in a linear regression model [21].

4. DISCUSSION

Evidence indicates that increases in serum lipids may be associated with decreases in symptoms in individuals with schizophrenia treated with antipsychotics, suggesting that serum lipids may be viable predictors of symptom improvement associated with antipsychotic treatment. Although some studies did not find a significant association, a closer look at each study may help narrow down our conclusion. In the following discussion, we aim to address several questions: 1) whether the relationship in question is direct and independent of other covariates, such as weight gain, 2) whether the relationship in question may be specific to certain antipsychotics, 3) whether interventions lowering serum lipids may worsen symptoms or affect antipsychotic response, and 4) what mechanisms may underlie the relationship in question.

4.1. Is the Relationship Independent of Weight Gain?

Nine studies included outcome measures that examined the relationship between changes in body weight, BMI, or waist circumference (in addition to changes in serum lipid concentrations) and changes in symptoms over time [8, 11, 12, 14-16, 19, 21, 22]. Six of these studies noted a significant inverse association [11, 12, 14-16, 22], which is consistent with previous findings [7]. A recent systematic review has found that 22 of the 33 included studies (67%) found an inverse association between antipsychotic-induced weight change and symptom change [7]. This is similar to our result in which 67% of the studies that examined such a relationship found a significant inverse association. However, it is of interest whether the association between increases in serum lipids and decreases in symptoms is independent of body weight.

Five of our included studies included body weight factors or other factors that promote weight gain (*i.e*., appetite) as covariates when analyzing the association between changes in serum lipids and changes in symptoms [8, 15, 16, 18, 21]. All five studies noted that the significance of the association

did not change after controlling for body weight factors. The study by Procyshyn *et al*. (2007) was the first to conduct a hypothesis-driven study to evaluate the significance of weight gain in the relationship between changes in serum lipids and changes in symptoms [8]. The authors did not find weight change to be associated with symptom change and this did not alter the significance of the association of increases in serum lipids with decreases in symptoms. Lally *et al*. (2013) performed a bivariate analysis and reported that a reduction in total PANSS scores was correlated with weight gain ($r = -0.32$, $p = 0.03$) and an increase in waist circumference ($r = -0.35$, $p = 0.01$) [15]. However, upon conducting a multiple linear regression analysis, body weight and waist circumference failed to reach statistical significance to predict PANSS score change [15]. Terevnikov *et al*. (2013) found significant inverse associations of weight gain with PANSS total score reduction in the FGA-mirtazapine group ($r = -0.48$, $p = 0.045$); however, body weight change was not a significant predictor in a linear regression model, whereas serum TC change was [16]. Sharma *et al*. (2014) found that increases in serum TG levels, but not appetite, significantly predicted BPRS score reduction [18]. Gjerde *et al*. (2018) did not find changes in BMI to be associated with changes in PANSS positive or negative subscale scores and this did not alter the significance of the association between increases in serum HDL-c concentrations and decreases in PANSS negative subscale scores [21].

In conclusion, serum lipids may predict antipsychotic response independent of weight gain.

4.2. Is the Relationship Specific to Certain Antipsychotics?

The association of increases in serum lipids with decreases in symptoms of schizophrenia may be specific to certain antipsychotics. First, this relationship may not be relevant to FGAs. Huang and Chen (2005) stratified their data further and found that participants who responded to SGAs demonstrated even greater increases in serum TG (+34.3 mg/dL, $p = 0.004$) and TC (+11.8 mg/dL, $p = 0.045$) levels, whereas those who responded to FGAs did not show any significant changes from baseline [13]. Terevnikov *et al*. (2013) did not find a significant association in the FGA-placebo group, but found a significant inverse association in the FGA-mirtazapine group [16]. The authors suggest that the SGA-like effects of mirtazapine, including raising serum TC levels, may be a reason for the presence of a significant association in the FGA-mirtazapine group [16]. Moreover, Luckhoff *et al*. (2018) found a significant association of increases in TG levels with decreases in PANSS disorganized symptoms in patients treated with flupenthixol decanoate, but failed to be a significant predictor in a linear regression model [22].

Second, not all SGAs seem to result in the same relationship. For instance, Garyfallos *et al*. (2003) noted a significant association between increases in serum TG levels and decreases in PANSS total scores in the olanzapine group, but not in the risperidone group [11]. Atmaca *et al*. (2003) noted a significant association between increases in serum TG levels and decreases in PANSS total scores in the clozapine and olanzapine groups, but not in the quetiapine or risperidone group [12]. This is consistent with the two studies that found a significant inverse association in clozapine-treated patients [8, 15]. The lack of significant association in the study by Hermes *et al*. (2011) may be explained by the fact that clozapine was not used in the study [14]. This study utilized perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone. However, it cannot be discounted that analyses were performed according to individual antipsychotics and still no significant associations were found. This indicates that the relationship may be less consistently found in patients treated with non-clozapine antipsychotics. Also, Gjerde *et al*. (2018) attributed the lack of significant association between changes in serum TG levels and changes in symptoms in their participants to the absence of clozapine use [21].

It should be noted, however, that Chukhin *et al*. (2016) did not find a significant relationship in 35 male participants treated with clozapine or olanzapine, of whom 18 received orlistat and 17 received placebo [19]. The lack of significant relationship could have been due to the influence of orlistat and a methodological factor. For instance, the authors did not use a complete dataset for their analysis as they included only the male participants who benefited from orlistat, excluding the 24 female participants who did not [19].

In conclusion, the association in question may be most relevant during treatment with clozapine.

4.3. Does Lowering Serum Lipids Affect Antipsychotic Response?

According to the relationship between increases in serum lipids and decreases in symptoms during antipsychotic treatment, it can be speculated that lowering serum lipids may have an impact on antipsychotic response and possibly lead to worsening of symptoms. Chukhin *et al*. (2016) were the first to conduct a hypothesis-driven study to examine whether orlistat-induced weight loss is associated with worsening of symptoms in individuals with schizophrenia [19]. Orlistat treatment did not worsen psychopathology in individuals treated with clozapine or olanzapine [19]. It was concluded that the interrelationship between antipsychotic-induced weight gain and symptom improvement may be indirect [19]. Therefore, it is of interest to evaluate the outcomes of pharmacological interventions (*e.g*., statins) that directly modulated serum lipids, which may be a stronger predictor of clinical response to antipsychotics than weigh gain.

As described above, Pande *et al*. (2002) reported a case in which a patient showing a good response to clozapine relapsed following a 7-week course of atorvastatin that significantly reduced his serum TG and TC concentrations [9]. Upon discontinuation of atorvastatin, the patient's serum TG and TC concentrations increased coinciding with a considerable improvement in his symptoms [9]. This implies that the lipid-lowering effects of statins may worsen the psychopathology of schizophrenia. With a similar rationale, other researchers have also raised a question of whether statin use might be safe in individuals with psychotic disorders [23].

To date, there have been several published reports on the efficacy of add-on statins (*i.e*., atorvastatin, lovastatin, pravastatin, and simvastatin) on the symptoms of schizo-

phrenia [24-29]. None of these trials reported worsening of symptoms associated with statin use. One possibility is that statins exert anti-inflammatory effects that may improve symptoms of schizophrenia [30, 31]. Perhaps, the anti-inflammatory effects of statins may negate the concomitant lipid-lowering effects that may have on the antipsychotic response. Nonetheless, the add-on effects of atorvastatin, lovastatin, and pravastatin on the symptoms of schizophrenia failed to reach significance in these trials [26-28].

According to a recent meta-analysis [32], the three simvastatin trials together significantly reduced negative symptoms [24, 25, 29], which seems to contradict the inverse association being discussed in this review. However, none of these trials reported whether simvastatin significantly reduced serum lipid concentrations. Also, only one simvastatin trial (*i.e*., the only simvastatin trial to report significant effects on negative symptoms) specified the antipsychotics the participants were taking, which was risperidone monotherapy [29]. As discussed above, Garyfallos *et al*. (2003) and Atmaca *et al*. (2003) did not find a significant inverse association in the risperidone-treated patients [11, 12], implying that response to risperidone may not be affected by changes in serum lipids.

None of the clinical trials to date have investigated the efficacy of statins strictly as an add-on to clozapine, whereas the case of atorvastatin-associated worsening of psychotic symptoms was reported in a clozapine-treated patient [9]. As the inverse relationship is most evident during clozapine treatment (Section 4.2), it is yet to conclude that statins do not lead to symptom exacerbation or do not affect clinical response to antipsychotics in patients with schizophrenia [33]. Therefore, future studies should investigate the add-on effects of statins in clozapine-treated patients.

One should also consider lifestyle modifications, such as healthy diet and exercise, as alternatives. For instance, physical exercise has both lipid-lowering and anti-inflammatory properties just like statins [34, 35] and has added benefits in the treatment of symptoms of schizophrenia [36]. Some studies have concomitantly examined the physical and mental health variables in individuals with schizophrenia receiving antipsychotics over the course of a supervised exercise program, finding that exercise-induced improvements in lipid profiles coincided with symptom improvement [37-39].

4.4. Mechanisms

Mechanisms underlying the association between increases in serum lipids and decreases in symptoms of schizophrenia during antipsychotic treatment are not clear. Previously, we suggested several potential mechanisms by which serum lipids may enhance antipsychotic response [8, 10]. One proposed mechanism suggests that serum lipids may alter the pharmacokinetics of antipsychotics. To this end, we have shown that clozapine redistributes itself from the lipoprotein-deficient fraction to the low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) fractions as serum TG concentrations increased [40]. This is in line with a recent study showing that lipophilic compounds with extensive hepatic metabolism (*e.g*., clozapine) have a strong tendency to associate with lipoproteins, in particular, LDL and VLDL [41]. Such an association can influence the transport, metabolism, and possibly the efficacy of drugs like clozapine by 1) creating a "physiological depot" from which the drug is released in a sustained manner comparable to the mechanism of action of depot antipsychotic medications and 2) facilitating the drug's penetration across the blood-brain barrier by passive diffusion or receptor-mediated processes [8, 41]. It is well established that some lipoproteins, including LDL, cross the blood-brain barrier by receptor-mediated transcytosis [42]. However, it needs to be further investigated *via* animal models or *in vitro* studies whether the interaction of clozapine with lipoproteins directly influences the efficacy of clozapine.

4.5. Limitations

There are several limitations to the available data. Many of the studies included in our review had small sample sizes and the amount of evidence still remains limited. However, the association between increases in serum lipids and decreases in symptoms of schizophrenia during antipsychotic treatment exists in all types of studies (observational, intervention, and case studies). With the exception of one study that used clozapine monotherapy [15], the use of antipsychotics was heterogeneous in our included studies. This heterogeneity may be a reason that studies found associations from different independent and dependent variables. For instance, Procyshyn *et al*. (2007) who included participants treated with either clozapine monotherapy or clozapine-risperidone polypharmacy found that serum TG and TC levels were inversely associated with PANSS negative subscale scores [8]. Lally *et al*. (2013) who included participants treated only with clozapine found that serum TG levels, but not TC, were inversely associated with both PANSS negative and positive subscale scores [15]. Nonetheless, the association between serum lipids and symptoms was still present with the heterogeneous use of antipsychotics [13, 16-18, 20, 21], indicating that serum lipids do play a role in some antipsychotic response in individuals with schizophrenia. Lastly, differences in clinical and demographic variables between studies cannot be neglected. Although the confounding variable of interest was body weight in our review, there can be other factors influencing the association of increases in serum lipids with decreases in symptoms of schizophrenia. These include factors that affect blood clozapine levels (*e.g*., compliance with antipsychotic treatment and cigarette smoking) as well as eating behavior or food intake. These confounding variables were inadequately reported and poorly controlled for across our included studies. Nonetheless, one study controlled for changes in serum clozapine levels and found a significant association between increases in serum TG levels and decreases in PANSS scores [15], and another study controlled for changes in appetite and found a significant association between increases in serum TG levels and decreases in BPRS scores [18].

CONCLUSION

Evidence suggests that increases in serum lipids may be associated with decreases in symptoms during antipsychotic treatment in individuals with schizophrenia and that serum

lipid may be viable predictors of antipsychotic response. The inverse association may be independent of confounding variables, such as weight gain. Also, the association in question may be most evident during treatment with dyslipidemia-inducing antipsychotics, such as clozapine. Recent trials investigating the add-on efficacy of statins in schizophrenia did not report any worsening of symptoms associated with statin use. This is optimistic as metabolic abnormalities, such as dyslipidemia, are serious health problems among individuals with schizophrenia and can be effectively treated with a variety of agents, including statins [43-47]. However, it still remains to be answered whether statins affect antipsychotic response by lowering serum lipids in clozapine-treated patients. Future studies should investigate this relationship in a larger population and identify molecular mechanisms that underlie this relationship.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

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