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The Effect of Antipsychotic Treatment on Hormonal, Inflammatory, and Metabolic Biomarkers in Healthy Volunteers: A Systematic Review and Meta-Analysis

Kyle Jon Burghardt[1,*], **Wasym Mando**[1], **Berhane Seyoum**[2], **Zhengping Yi**[3], **Paul Ryen Burghardt**[4]

[1]Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan

[2]Division of Endocrinology, School of Medicine, Wayne State University, Detroit, Michigan

[3]Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan

[4]Department of Food and Nutrition Sciences, College of Literature Arts and Sciences, Wayne State University, Detroit, Michigan

Abstract

Antipsychotic medications demonstrate a variable range of efficacy and side effects in patients with mental illness. Research has attempted to identify biomarkers associated with antipsychotic effects in various populations. Research designs utilizing healthy volunteers may have the added benefit of measuring the effect of antipsychotics on a given biomarker(s) independent of the varied environmental and clinical factors that often accompany patient populations. The aim of this systematic review and meta-analysis was to synthesize the current evidence of hormonal, inflammatory, and metabolic biomarker studies of antipsychotic treatment in study designs using healthy volunteers. The systematic review was performed according to established guidelines and a random effects meta-analysis of biomarkers appearing in at least three studies was performed while biomarkers in two or less studies were qualitatively summarized. A total of 28 studies including 28 biomarkers were identified. Meta-analyses were carried out for 14 biomarkers, showing significant effects within 6 biomarkers (cortisol, C-peptide, free fatty acids, leptin, thyroid-stimulating hormone and prolactin). Many of these effects were associated with olanzapine, the most used antipsychotic amongst the trials, observed on sub-analyses. When combining biomarkers into categories, some additional effects were observed, for example, when grouping inflammatory biomarkers. These findings suggest that antipsychotics exert potentially strong effects on several biomarkers of interest independent of psychiatric disease which could be used to spur future investigations, however, replication work is needed for many biomarkers included in this review.

[*]Correspondance: 259 Mack Avenue Suite 2190, Detroit, MI 48201; kburg@wayne.edu.

Conflict of Interest

The authors have no conflict of interests to declare

Keywords

Antipsychotic; biomarker; inflammatory; metabolic; hormonal; meta-analysis

Introduction

Antipsychotics are a pharmacotherapeutic option for severe mental illness that includes schizophrenia and bipolar disorder. Although the primary receptor targets of these medications are dopamine and serotonin, their receptor profiles can vary greatly. Coupled with a large volume of distribution, which is critical for their therapeutic effects after crossing the blood brain barrier, this can also lead to side effects. Considerable research has been performed with the aim of identifying biomarkers of therapeutic benefit and side effects of antipsychotics.

Biomarkers have the ability to provide important information for treatments as they could allow for estimation of likelihood of treatment benefit and side effects and offer a tool in the pursuit of precision medicine.[1] Additionally, biomarkers could aid in the development of newer treatments that aim at retaining beneficial effects while reducing or removing side effects. Several biomarkers have been investigated in respect to antipsychotic treatment. These include biomarkers such as prolactin with sexual side effects and leptin with weight gain.[2,3] These studies include various designs such as case control and randomized controlled trials and varied populations such as patients with schizophrenia and healthy controls.

Despite these investigations, there has not been an in-depth synthesis and evaluation of biomarkers in healthy volunteers (i.e., free from both physical and mental illness) treated with antipsychotics. The use of healthy volunteer trials may clarify the direct effects of antipsychotics as it reduces some potential sources of bias that can be found in psychiatric populations including comorbid disease states that may independently affect biomarkers of interest.[4] The objective of this systematic review and meta-analysis was to produce a comprehensive report on the effects of antipsychotics on inflammatory, metabolic, and/or hormonal biomarkers in healthy volunteer studies to better inform future work in antipsychotic biomarker development.

Methods

Study Search Strategy, Eligibility Criteria, Data Extraction

To answer our systematic review question of, “What is the effect of antipsychotic treatment on hormonal, inflammatory, and/or metabolic biomarkers in healthy volunteers?”, we performed searches in Medline, Web of Science, and Embase databases. Searches included combinations of the following words: antipsychotic, hormone, metabolic, inflammatory, inflammation, healthy, biomarker, and marker. Limits placed on the search included filtering to human studies and excluding reviews. Additionally, specific terms for antipsychotics (e.g., “olanzapine”, “quetiapine”, etc.) and relevant biomarkers commonly studied, based on our knowledge (e.g., “cortisol”, “IL-6”, etc.), were entered into the searches as well.

Searches were performed from earliest data in each database until July 2021 according to PRISMA guidelines and the systematic review protocol was registered at PROSPERO (CRD42020204418).

Search results were imported into Covidence software for duplicate removal and screening against the following inclusion criteria: 1) reports a hormonal, inflammatory, or metabolic measure (insulin was not included as this has already been studied in a meta-analysis of healthy volunteers[5]), 2) utilizes a placebo or no intervention control group, 3) study population is healthy volunteers based on defined inclusion/exclusion criteria within study, 4) necessary data for meta-analysis available from article or upon request from authors, and 5) English language article. Records were excluded if they were 1) non-human studies, 2) reviews or commentaries, and 3) performed in non-healthy populations (e.g., psychiatric populations, etc.). Two reviewers independently screened the records with disagreements resolved by consensus.

For studies meeting inclusion criteria, the following data were extracted: 1) citation and author information, 2) trial design type, 3) blinding type in study, 4) control group type, 5) antipsychotic(s) and dose(s) utilized in study, 6) number of participants in study, 7) sex, 8) age, and 9) data related to biomarker(s) measured in study. Extraction for each biomarker included data such as means with standard deviation (SD). If standard deviation was not provided it was calculated from available data such as a 95% confidence interval or standard error according to the Cochrane Handbook for Systematic Reviews (e.g., SD = SE × SQRT(N), etc.).[6] For computation of standard deviation of changes from baseline, we utilized: $SD_{change} = SQRT\ (SD^2_{baseline} + SD^2_{final} – (2 \times Corr \times SD_{baseline} \times SD_{final}))$ where Corr is the correlation coefficient which refers to how similar baseline and final measurements were across studies. Often the correlation coefficient cannot be calculated so it was assumed at a conservative 0.4 which is used in other meta-analyses.[7] If data was only available in a figure, the image was uploaded into WebPlotDigitizer version 4.5 (https://automeris.io/WebPlotDigitizer) and then extracted.

Assessment of Study Quality and Bias

Study quality was assessed with the Cochrane Risk of Bias 2.0 tool. The cross-over version of the tool was used for applicable studies. Additionally, the Jadad scale was used as a secondary assessment of study quality. Publication bias was assessed by funnel plots, the Egger’s test, and the trim and fill method.

Data Analysis

For biomarkers that were replicated in three or more independent studies, we performed a random effects meta-analysis with pooled results in Comprehensive Meta-Analysis (CMA) software version 3. Although no official cutoff is proposed, a theoretical minimum of two studies is suggested for performing a quantitative meta-analysis.[8] We chose to meta-analyze biomarkers with three or more studies as this allowed for us to calculate meta-analytic effect sizes for many markers of interest while ruling out less commonly studied biomarkers that may include power or bias issues. Effect sizes were calculated with a standardized mean difference (SMD) in CMA with standard error (se). An SMD was calculated based

on the data available for each included study such as 1) baseline and end point values, 2) change in values, or 3) end point values (i.e., for crossover studies). When a study included multiple antipsychotics compared to a control group, the computed, pooled value of all antipsychotics was used for that study to calculate a summary effect size.[9] When biomarkers were combined for a test of all biomarkers or based on category, the absolute value of the SMD was taken to account for the potential opposite direction of change for a given biomarker. For example, in our results leptin had a positive SMD while ghrelin had a negative SMD, but when combined in the category of "food regulation", the absolute values were taken to estimate a general effect. For the individual biomarker analysis, the true direction of antipsychotic effect (positive or negative SMD) was utilized. A random effects meta-analysis was performed for all biomarkers, each biomarker individually, biomarkers by category, and based on antipsychotic type using a 2-sided test with statistical significance set at $P<0.05$. Heterogeneity was estimated with I^2 and Q values with an $I^2> 50\%$ and $P<0.05$ considered to have significant heterogeneity. The primary study details and meta-analysis results are detailed in quantitative tables included in the main manuscript in order to provide the key findings of each analysis. The quality control figures (i.e., trim and fill plots) are included for in-depth review in the supplementary material.

For biomarkers that were evaluated in one or two studies, and not included in the meta-analysis described above, descriptive statistics were provided that included a calculated Hedge's g statistic. Large effect sizes were defined by a Hedge's g greater than 0.8, medium effect sizes by a Hedge's g of 0.2 to 0.79, and small to no effects was defined by a Hedge's g below 0.2.

Results:

Within the 28 included studies (see PRISMA diagram in supplementary figure 1), a total of 28 biomarkers, including hormonal, inflammatory, and metabolic, were analyzed. Prolactin was the most studied biomarker (16 studies), followed by cortisol (12 studies), leptin (7 studies), and free fatty acids (FFA, 6 studies). Adiponectin, C-peptide, growth hormone (GH), ghrelin, interleukin-6 (IL-6), luteinizing hormone (LH), and thyroid stimulating hormone (TSH) were all analyzed in four studies each. Olanzapine was the most used antipsychotic and was given in 15 studies. The next most used antipsychotics were haloperidol (6 studies) and quetiapine (3 studies). All other antipsychotics were used in two or less studies. The longest treatment length was 30 days (1 study) with the shortest being a single dose (10 studies). The quality assessments of the included studies using the Cochrane Risk of Bias 2.0 and Jadad scale identified some concerns due primarily to a lack of availability of a clinical trial protocol to assess pre-specified protocol adherence or due to single blinding within a study. An overview of the studies can be found in Table 1.

Meta-Analyses

Combined and Individual Biomarker Analysis—All biomarkers replicated within at least three studies were meta-analyzed to estimate an overall effect of antipsychotic on these measures. The random effects analysis of 27 eligible studies (one study[26] investigating gastric inhibitory polypeptide and pancreatic polypeptide was not included as it was the only

study to include these biomarkers) showed a significant effect of antipsychotic treatment on all combined biomarkers (SMD = 0.749, se = 0.093, P<0.001, I^2=38.5%). Meta-analyses were then performed for each biomarker replicated in at least three studies. This included 14 individual biomarkers of which, 6 showed a significant association with antipsychotic treatment. These six significant associations were for cortisol, C-peptide, FFA, leptin, TSH and prolactin. Heterogeneity estimates ranged from not detectable (<1%) to high (64%) which was dependent on the individual biomarker. Publication bias evaluation by the Eggers test indicated possible bias in the combined biomarker and FFA analyses. A summary of meta-analyses is provided in Table 2 while funnel plots with trim and fill results are presented in the supplementary results.

Sub-Analyses

Biomarker Analysis by Category: Next, meta-analyses were performed by grouping biomarkers together in categories based primarily on their function, including food regulation, sex hormones, adrenal hormones, pituitary hormones, inflammatory, insulin/diabetes, and thyroid. The results for this grouping sub-analysis are shown in Table 3. This analysis yielded significant meta-analytic results for all biomarker categories except for the category of sex hormones.

Analysis by Individual Antipsychotic: As described above, several antipsychotics were used amongst the included studies. Given the possible heterogeneity caused by different antipsychotics having distinct receptor profiles, we performed the biomarker analyses restricted to antipsychotics used in three or more replications. At least one biomarker was measured after aripiprazole, haloperidol, and/or olanzapine treatments in three separate studies. This includes prolactin for aripiprazole, and cortisol and prolactin for haloperidol. The biomarkers that were available for olanzapine were adiponectin, cortisol, c-peptide, FFA, ghrelin, glucagon, IL-6, leptin, prolactin, and tumor necrosis factor alpha (TNFα). The biomarkers that were significantly changed by these individual antipsychotic sub-analyses can be found in Table 4.

Qualitative Description of Other Biomarkers—For the included studies of biomarkers that were explored in only one or two studies, and therefore not included in the quantitative meta-analysis, an overview of the results is provided in Table 5. This includes 13 biomarkers. Eight were studied in 2 independent studies, generally showing mixed results whereas the remaining five were included in only one study. Olanzapine was administered as the antipsychotic in the highest number (7) of the qualitative biomarkers followed by sulpride, quetiapine, haloperidol, and risperidone. Adrenocorticotropic hormone (ACTH) showed a large effect size (decrease) in one study withquetiapine, although another study showed a medium effect size in the opposite direction. Similarly, dehydroepiandrosterone (DHEA) showed a large effect size decrease and thyroxine (T4) showed a large effect size increase with sulpride, while, in both cases, another study found no effect of sulpride on these biomarkers.

Discussion

This meta-analysis found that several hormonal and metabolic biomarkers are altered by antipsychotic treatment in healthy volunteers. Namely, cortisol, c-peptide, FFA, leptin, prolactin, and TSH showed a significant association with antipsychotic treatment. Our analyses found no effect of antipsychotic treatment on inflammatory biomarkers at the individual level. When inflammatory biomarkers were grouped together, however, there was a statistically significant effect. These effects were confirmed to be associated with olanzapine use (except for TSH which was not studied with olanzapine) in our sub-group analyses which is attributable to the fact that olanzapine was the most used antipsychotic within these healthy volunteer studies. Finally, our qualitative synthesis of biomarkers showed few large effects and many mixed findings but potential for follow-up in future studies. Below we review some of the key biomarker findings from this meta-analysis and discuss details including potential mechanisms and similar biomarker studies in psychiatric population studies. These comparisons to psychiatric population biomarker studies do not extend the findings of the studies of healthy volunteers included here but rather provide background for similar biomarker work in psychiatric populations treated with antipsychotics that can be used to inform future work.

Biomarkers Involved in Food Regulation and Diabetes

The results here indicate that in healthy volunteers, C-peptide and leptin were significantly increased after antipsychotic treatment whereas FFA was significantly decreased. Additionally, the grouped biomarker analysis showed significant antipsychotic effects on both biomarker groups (food regulation and insulin/diabetes). Biomarkers and pathways of food regulation and diabetes are an active area of research due to antipsychotic metabolic side effects which include weight gain, dyslipidemia, insulin resistance, diabetes, and cardiovascular disease.[38] C-peptide is part of the proinsulin hormone that is removed when the body converts proinsulin to insulin. It is thought to be an important marker of endogenous insulin production by beta cells and in understanding the pathology of diabetes. Within the studies included here, antipsychotic treatment increased c-peptide levels and thus insulin production which has also been identified in studies of psychiatric patients and healthy volunteers treated with antipsychotics .[39,40] The hypothesized mechanisms by which antipsychotics increase c-peptide concentrations could be through muscarinic, serotonergic, and dopaminergic activity.[41,42] As a biomarker, FFAs are correlated with insulin resistance and are posited to mediate the link between obesity and diabetes, and are generally increased in individuals with diabetes.[43] The decreased FFAs identified here may be reflective of the acute treatment (1 month or less) in healthy volunteers which may not have the treatment length necessary for the significant weight gain to cause an increase in FFAs released from adipocytes. Psychiatric populations treated with antipsychotic have also found increased FFAs with long-term treatment.[44] The proposed effects of FFA are mediated through the PI3K/AKT pathway therefore their decrease in the short-term studies included here is likely not explanatory for other studies showing acute insulin resistance cause by antipsychotics in healthy volunteers.[40,43] Finally, leptin, a neurohormone involved in food regulation, was also increased in this meta-analysis. Increased leptin inhibits hunger but its dysregulation and resistance are found in obesity, insulin resistance, and diabetes. Similar to the findings

presented here in healthy volunteers, leptin is shown to be elevated with antipsychotic treatment in psychiatric populations.[45]

Hormonal Biomarkers

Several hormonal biomarkers were associated with antipsychotic use in this meta-analysis including prolactin, cortisol, and TSH. Prolactin is well-studied in terms of antipsychotic treatment and the findings here of increased levels in healthy volunteers are in line with a large, existing body of work showing increases in prolactin levels following treatment from most antipsychotics in psychiatric populations.[2,46] There was a meta-analysis from 2001 that predicted the prolactin-inducing dose curve in healthy volunteers primarily from pharmaceutical trial data.[47] This analysis pointed to most antipsychotics causing hyperprolactinemia with some, such as haloperidol, risperidone, and fluphenazine, having a more pronounced effect than others. Cortisol, a glucocorticoid hormone with a role in many processes including stress and inflammation, was identified to be decreased following antipsychotic treatment in healthy volunteers. It may be that this decrease reflects a therapeutic effect of antipsychotics. Meta-analyses have identified increased cortisol levels in individuals with first-episode psychosis not yet treated with antipsychotics.[48] Consistent with this hypothesis, antipsychotic treatment is associated with a blunted cortisol response to stress and cortisol levels are found to be higher in treated patients with schizophrenia compared to healthy controls. In contrast, other groups report no effect of antipsychotics on cortisol in long-term treated patients.[49,50] Taken together, antipsychotic do appear to have an effect on cortisol but future work in psychiatric populations will be needed to understand acute versus long-term changes. Finally, TSH was found to be increased in the analyses presented here. In one study., acute treatment (mean duration of 29 days) of psychosis with antipsychotics increased TSH levels.[51] Similarly, in a retrospective study , an increase in TSH was observed following greater than 2 months of antipsychotic treatment.[52] In contrast, additional work has found increased levels of TSH in schizophrenia patients after a median of 3.5 months of treatment versus healthy controls but this increase did not correlate with antipsychotic use.[53] Thus, there appears to be evidence for an effect on thyroid measurements in both healthy volunteer and psychiatric antipsychotic treatment studies.

Inflammatory Biomarkers

Although no individual inflammatory biomarker was significantly altered by antipsychotic use in the meta-analysis, the grouped analysis including CRP, IL-6, and TNFα found a significant association with antipsychotic use. A possible reason for this “group” effect could be the overall limited number of studies on an individual inflammatory biomarker and the subsequent increased power by combining the biomarkers into a group. Inflammatory markers including CRP were evaluated in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial which found that in those with low baseline CRP levels, olanzapine was associated with a significant increase in CRP levels which correlated with metabolic side effects.[54] Similar work has identified decreases in IL-6 and TNFα after 7 months of antipsychotic treatment in first episode psychosis patients.[55] Meta-analyses of inflammatory biomarkers in several populations treated with antipsychotics yield mixed

findings which appear dependent on length of treatment, history of previous treatment, and baseline levels which are associated with disease severity.[56–60] The findings here in healthy volunteers undergoing short-term antipsychotic treatment add to this evidence base, however, more work is needed to understand this complex pathway of effects on inflammatory biomarkers and the potential, direct effect of antipsychotics in healthy volunteer populations.

Limitations

A few limitations of this meta-analyses should be considered. First, although the overall number of studies included was reasonable, the number of studies for each of the individual biomarkers was small in most cases. Additionally, the sample sizes for each individual study were smaller and of limited treatment duration possibly due to the nature of treating healthy volunteers with an antipsychotic. Furthermore, as 10 studies were only evaluating a single dose, it is conceivable that extended durations of treatment could change biomarkers that were not changed with a single dose. Future work could include longer treatment durations with multiple measurement points to understand this effect. The healthy volunteer population included here limits generalizability and cannot capture baseline states in psychiatric populations that could influence how the biomarker responds to antipsychotic treatment (e.g., increased cortisol in antipsychotic-naive patients, etc.,), however, it does give a view of the effects of antipsychotics in humans without the potential heterogeneity that can be found in psychiatric population studies (e.g., past medical histories, medication histories, etc.,). Furthermore, the quality of most studies was moderate with some concerns and heterogeneity in some of the biomarkers analyses was high and statistically significant. Finally, although some of the detected effects in this meta-analysis produced P-values <0.01, this threshold should be taken with caution as many statistical tests were performed.

Conclusion

The findings here help to synthesize and provide estimates to the numerous studies that aim to identify biomarkers and their pathways that are associated with antipsychotic treatment in healthy population study design. Some of these findings are supported in studies of psychiatric populations that are treated with antipsychotics. Nevertheless, for many of the biomarkers identified here, further replication is required to understand the effects of antipsychotics and to solidify them as biomarkers that can be used to tailor or monitor antipsychotic treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Characteristics of Included studies.

Study	Biomarker (s)	Number of subjects	Antipsychotic (s)	Trial Length (days)	Risk of Bias[a]
Albaugh 2011[10]	Leptin	15	Olanzapine	3	Low
Ballon 2018[11]	Adiponectin, cortisol, c-peptide, GH, glucagon, IL-6, leptin, TNFα	24	Iloperidone, Olanzapine	28	Low
Baptista 1997a[12]	Cortisol, DHEA, E2, FSH, LH, prolactin, testosterone, T4, TSH	14	Sulpride	30	Some concerns
Baptista 1997b[13]	Cortisol, DHEA, E2, FSH, LH, progesterone, prolactin, testosterone, T4, TSH	34	Sulpride	28	Some concerns
Cohrs 2004[14]	Cortisol, melatonin	13	Quetiapine	2	Some concerns
Cohrs 2006[15]	ACTH, cortisol, prolactin	11	Haloperidol, Olanzapine, Quetiapine	1	Some concerns
Daurignac 2015[16]	Leptin	19	Olanzapine	14	Some concerns
de Borja Gonçalves Guerra 2005[17]	ACTH, cortisol, GH, prolactin	15	Quetiapine	1	Some concerns
Fountaine 2010[18]	Adiponectin, cortisol, CRP, ghrelin, IL-6, leptin, prolactin, TNFα	21	Olanzapine	15	Some concerns
Hahn 2013[19]	Adiponectin, cortisol, c-peptide, CRP, FFA, IL-6, leptin, prolactin, TNFα	15	Olanzapine	1	Some concerns
Handley 2016[20]	Cortisol, IL-6	17	Aripiprazole, Haloperidol	1	Some concerns
Lee 1995[21]	Prolactin	10	Clozapine, Haloperidol	1	Some concerns
Liem-Moolenaar 2010[22]	Cortisol, FSH, LH, prolactin	22	Haloperidol	1	Some concerns
Mallikaarjun 2004[23]	Prolactin	38	Aripiprazole	14	Some concerns
Nahmias 2020[24]	FFA, prolactin	8	Olanzapine	1	Some concerns
Pretorius 2001[25]	prolactin	12	Clozapine, Haloperidol	1	Low
Rickels 2018[26]	GIP, PP	15	Olanzapine	9	Some concerns
Roerig 2008[27]	Ghrelin	28	Olanzapine, Risperidone	14	Low
Samuels 2006[28]	Prolactin, TSH	16	Amisulpride	1	Some concerns
Sowell 2002[29]	C-peptide	48	Olanzapine, Risperidone	15–17	Some concerns
Sowell 2003[30]	FFA	55	Olanzapine, Risperidone	21	Some concerns
Teff 2013[31]	C-peptide, ghrelin, glucagon, GLP-1, leptin	30	Aripiprazole, Olanzapine	9	Some concerns
Veselinović 2011[32]	Prolactin	54	Haloperidol	7	Some concerns
Veselinović 2018[33]	Prolactin	54	Aripiprazole, Haloperidol	7	Some concerns
Vidarsdottir 2009[34]	Cortisol, prolactin	12	Olanzapine	8	Low

Study	Biomarker (s)	Number of subjects	Antipsychotic (s)	Trial Length (days)	Risk of Bias[a]
Vidarsdottir 2010a[35]	CCK, ghrelin, GLP-1, glucagon, PP, PYY	10	Olanzapine	8	Low
Vidarsdottir 2010b[36]	Adiponectin, FFA, leptin	12	Olanzapine	8	Low
Wetzel 1994[37]	Cortisol, GH, LH, prolactin, TSH	8	Amisulpride	1	Some concerns

Abbreviations: ACTH=Adrenocorticotropic hormone; CCK= Cholecystokinin; CRP=c-reactive protein; DHEA=Dehydroepiandrosterone; E2=estrogen; FFA=free fatty acid; FSH=follicle stimulating hormone; GIP=Gastric inhibitory polypeptide; GH=growth hormone; GLP-1=Glucagon Like Peptide-1; LH=luteinizing hormone; IL-6=interleukin-6; PAI=Plasminogen activator inhibitor; PP=pancreatic polypeptide; PYY=peptide YY; T4=thyroxine; TNFα=tumor necrosis factor alpha; TSH=thyroid stimulating hormone

[a]see supplementary data for full evaluations.

Table 2.

Meta-analyses of combined and individual biomarkers.

Biomarker	Number of studies	Antipsychotics	SMD (se)	P-value	I^2 (%)	Egger's
All	**27**		**0.749 (0.093)**	**<0.001**	**38.5** *	**0.003**
Adiponectin	4	Iloperidone, Olanzapine	0.346 (0.262)	0.187	63.2*	0.972
Cortisol	12	Amisulpride, Aripiprazole, Haloperidol, Iloperidone, Olanzapine, Quetiapine, Sulpride	−0.499 (0.150)	<0.001	59.6*	0.226
C-peptide	4	Aripiprazole, Iloperidone, Olanzapine, Risperidone	0.546 (0.214)	0.011	22.6	0.589
FFA	6	Aripiprazole, Olanzapine, Risperidone	−0.418 (0.143)	0.004	8.7	0.0435
FSH	3	Haloperidol, Sulpride	0.157 (0.174)	0.366	<1	0.189
GH	4	Amisulpride, Olanzapine, Iloperidone, Quetiapine	−0.087 (0.163)	0.595	<1	0.904
Ghrelin	4	Aripiprazole, Olanzapine, Risperidone	−0.257 (0.170)	0.131	<1	0.204
Glucagon	3	Aripiprazole, Iloperidone, Olanzapine	0.299 (0.246)	0.224	<1	0.890
IL-6	4	Aripiprazole, Haloperidol, Iloperidone, Olanzapine	−0.033	0.825	10.3	0.823
Leptin	7	Aripiprazole, Iloperidone, Olanzapine	0.300 (0.122)	0.014	<1	0.556
LH	4	Amisulpride, Haloperidol, Sulpride	0.155 (0.158)	0.326	<1	0.412
Prolactin	16	Amisulpride, Aripiprazole, Clozapine, Haloperidol, Olanzapine, Quetiapine, Sulpride	1.23 (0.228)	<0.001	77.1*	0.859
TNFα	3	Iloperidone, Olanzapine	−0.297 (0.235)	0.207	43.9	0.815
TSH	4	Amisulpride, Sulpride	1.091 (0.400)	0.006	64.2*	0.144

Random effects analyses include standardized mean differences with standard error, P-value, percent heterogeneity, and Egger's P-value calculated for combined and individual biomarker. Combined biomarker analysis uses absolute values for effect size calculation while individual biomarker analyses reflect direction of antipsychotic effect on a given biomarker.

* indicates heterogeneity defined as I^2>50% and P<0.05

Abbreviations: FFA=free fatty acid; FSH=follicle stimulating hormone; GH=growth hormone; IL-6=interleukin-6; LH=luteinizing hormone; TNFα=tumor necrosis factor alpha; TSH=thyroid stimulating hormone

Table 3.

Meta-analyses of biomarker category.

Category	Biomarkers	Number of studies	SMD (se)	P-value	I^2	Egger's
Food Regulation	Adiponectin, CCK, Ghrelin, Leptin, PP, PYY	10	0.377 (0.111)	<0.001	<1	0.342
Sex Hormones	E2, FSH, LH, testosterone, Progesterone	4	0.217 (0.158)	0.170	<1	0.547
Adrenal Hormones	Cortisol, DHEA	12	0.570 (0.133)	<0.001	48.5*	0.052
Pituitary Hormones	ACTH, GH, Prolactin	17	1.247 (0.149)	<0.001	52.8*	0.011
Inflammatory	CRP, IL-6, TNFα	4	0.347 (0.140)	0.013	<1	0.921
Insulin/Diabetes	C-peptide, FFA, GIP, GLP-1, Glucagon	10	0.492 (0.114)	<0.001	<1	0.931
Thyroid	T4, TSH	4	1.16 (0.450)	0.010	71.2*	0.204

Random effects analyses include standardized mean differences with standard error, P-value, percent heterogeneity, and Egger's P-value calculated for combined and individual biomarker. Category analyses use absolute values for effect size calculation while individual biomarker analyses reflect direction of antipsychotic effect on a given biomarker.

*indicates heterogeneity defined as I^2>50% and P<0.05

Abbreviations: ACTH=Adrenocorticotropic hormone; CCK= Cholecystokinin; CRP=c-reactive protein; DHEA=Dehydroepiandrosterone; E2=estrogen; FFA=free fatty acid; FSH=follicle stimulating hormone; GIP=Gastric inhibitory polypeptide; GH=growth hormone; GLP-1=Glucagon Like Peptide-1; LH=luteinizing hormone; IL-6=interleukin-6; PP=pancreatic polypeptide; PYY=peptide YY; T4=thyroxine; TNFα=tumor necrosis factor alpha; TSH=thyroid stimulating hormone

Table 4.

Meta-analyses of biomarkers by individual antipsychotics.

Antipsychotic	Biomarkers	Number of studies	SMD (se)	P-value	I^2
Aripiprazole	Prolactin	3	−0.978 (0.895)	0.275	91.9*
Haloperidol	Cortisol	3	−0.236 (0.215)	0.273	51.8
Haloperidol	Prolactin	6	1.358 (0.156)	<0.001	<1
Olanzapine	Adiponectin	4	0.323 (0.264)	0.222	63.8*
Olanzapine	Cortisol	5	−0.794 (0.256)	0.002	62.6*
Olanzapine	C-peptide	4	0.604 (0.227)	0.008	30.7
Olanzapine	FFA	4	−0.492 (0.134)	<0.001	<1
Olanzapine	Ghrelin	4	−0.252 (0.170)	0.137	<1
Olanzapine	Glucagon	3	0.424 (0.285)	0.136	22.3
Olanzapine	IL-6	3	−0.023 (0.238)	0.924	46.3
Olanzapine	Leptin	7	0.317 (0.122)	0.009	<1
Olanzapine	Prolactin	5	1.443 (0.230)	<0.001	33.3
Olanzapine	TNFα	3	0.313 (0.232)	0.178	42.5

Random effects analyses include standardized mean differences with standard error, P-value and percent heterogeneity.

* indicates heterogeneity defined as I^2>50% and P<0.05

Abbreviations: FFA=free fatty acid; IL-6=interleukin-6; TNFα=tumor necrosis factor alpha

Table 5.

Summary of Biomarkers Not Included in Meta-Analysis.

Hormone/Inflammation	Number of studies	Antipsychotics (effect on biomarker)
ACTH	2	Haloperidol (↔), Olanzapine (↓), Quetiapine(↓*,↑)
CCK	1	Olanzapine (↑)
CRP	2	Olanzapine (↓,↔)
DHEA	2	Sulpride (↓*,↔)
E2	2	Sulpride (↓,↓)
GIP	1	Olanzapine (↑)
GLP-1	2	Olanzapine (↑,↔), Risperidone (↓)
Melatonin	1	Quetiapine (↔)
PP	2	Olanzapine (↑,↔)
Progesterone	1	Sulpride (↓)
PYY	1	Olanzapine (↔)
Testosterone	2	Sulpride (↔)
T4	2	Sulpride (↑*,↔)

↓* or ↑* indicates direction of effect of antipsychotic with a large effect size defined by a Hedges g greater than 0.8. ↓ or ↑ indicates direction of effect of antipsychotic with a medium effect size defined by a Hedges g of 0.2 to 0.79. ↔ indicates small to no effect with a Hedges g below 0.2.

Abbreviations: ACTH=Adrenocorticotropic hormone; CCK= Cholecystokinin; CRP=c-reactive protein; DHEA=Dehydroepiandrosterone; E2=estrogen; GIP=Gastric inhibitory polypeptide; GLP-1=Glucagon Like Peptide-1; PAI=Plasminogen activator inhibitor; PP=pancreatic polypeptide; PYY=peptide YY; T4=thyroxine