

Hormonal changes

Introduction

Hormones are chemical messengers secreted by the endocrine glands. Hormones travel through the bloodstream to tissues and organs, and control most of the body's major systems including heart rate, metabolism, mood, sexual function, and growth and development.

Neuroactive steroids, including testosterone, dehydroepiandrosterone (DHEA) and its sulphide ester (DHEA-S), are important for brain development as they influence synaptic connectivity and neuronal differentiation. They influence dopaminergic, glutamatergic, and GABAergic neurotransmission that have been found to be dysregulated in schizophrenia.

Estrogen has been proposed to confer a protective effect for schizophrenia. Women generally have a later onset of schizophrenia than males with an increased risk after menopause (see the risk factor topic on sex differences). Estrogen levels drop over time, particularly with the onset of menopause. This protection may also mean that pre-menopausal women who develop schizophrenia may experience a less severe illness than males.

Prolactin is another hormone implicated in schizophrenia. It is a polypeptide secreted by the pituitary gland, and is involved in many biological functions including reproduction, pregnancy and lactation, and growth and development. Some medications, such as antipsychotics are among the factors that can affect blood prolactin concentrations. Increased prolactin (hyperprolactinemia) is associated with a variety of adverse effects, including risk of breast cancer, lack of menstruation, and early osteoporosis in women, and a lack of libido and erectile function in men.

Body weight is regulated by anorexigenic or appetite suppressing hormones (e.g. insulin, leptin, peptide YY, and cholecystokinin) and orexigenic or appetite stimulating hormones (e.g. neuropeptide Y, orexins, agouti-related

peptide, galanin, and ghrelin). These hormones are mostly produced by adipose tissue (e.g. adiponectin, leptin, resistin, vaspin and visfatin) or by the gastrointestinal tract (e.g. cholecystokinin, glucagon-like peptide 1, ghrelin and peptide YY). Alterations in the production of appetite-regulating hormones might be present in psychotic disorders.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis¹. Reviews rated as having less than 50% if items checked are excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development

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and Evaluation ([GRADE](#)) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)². The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

olanzapine may show reduced adiponectin levels. Adiponectin, ghrelin, orexin, resistin, and visfatin were not altered in people with first-episode psychosis.

- Moderate quality evidence suggests a large increase in prolactin levels in antipsychotic-naïve males with schizophrenia and a medium-sized increase in antipsychotic-naïve females with schizophrenia.
- Moderate quality evidence finds a medium to large effect of elevated DHEA-S levels in people with schizophrenia compared to controls. Testosterone levels were elevated only in first-episode psychosis patients and in patients in an acute relapse. There were no differences in DHEA.
- We found no systematic review assessing estrogen levels in people with schizophrenia.

Results

We found seven systematic reviews that met our inclusion criteria³⁻⁹.

- Moderate to high quality evidence finds a small to medium-sized increase in leptin levels in people with chronic schizophrenia compared to controls, particularly in patients taking second generation antipsychotics olanzapine and clozapine.
- Moderate to high quality evidence finds a small to medium-sized effect of higher insulin levels and a trend effect of lower leptin levels in people with first-episode psychosis compared to controls. These effects were both significant in subgroup analyses of antipsychotic-naïve patients. The severity of negative symptoms was associated with increased effect size estimates for insulin.
- Moderate to high quality evidence finds no differences in adiponectin levels between people with schizophrenia and controls, although patients taking clozapine or

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Bartoli F, Lax A, Crocamo C, Clerici M, Carra G

Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: a meta-analysis

Psychoneuroendocrinology 2015; 56: 179-89

[View review abstract online](#)

Comparison	Adiponectin levels in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples inconsistent, precise, direct) suggests no differences in adiponectin levels, although patients taking clozapine or olanzapine may show reduced levels.
Adiponectin	
<p><i>There were no significant differences between groups;</i> 18 studies, N = 2,735, SMD = -0.28, 95%CI -0.59 to 0.04, $p = 0.09$, $I^2 = 91\%$ Subgroup analysis showed patients taking clozapine and olanzapine showed reduced adiponectin levels. There were no differences in subgroup analysis of drug free/drug naïve subjects.</p>	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Fraguas D, Diaz-Caneja CM, Ayora M, Hernandez-Alvarez F, Rodriguez-Quiroga A, Recio S, Leza JC, Arango C

Oxidative stress and inflammation in first-episode psychosis: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2019; 45(4): 742-51

[View review abstract online](#)

Comparison	DHEA-S in people with first-episode psychosis vs. controls.
Summary of evidence	Moderate to low quality evidence (small sample, unable to assess consistency, imprecise, direct) finds no differences in DHEA-S levels in people with first-episode psychosis.

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DHEA-S	
<p><i>No significant differences between groups;</i> 3 studies, N = 163, $d = 0.449$, 95%CI -1.014 to 1.912, $p > 0.995$, I^2 not reported</p>	
Consistency in results	Unable to assess consistency.
Precision in results	Imprecise
Directness of results	Direct

Gonzalez-Blanco L, Greenhalgh AM, Garcia-Rizo C, Fernandez-Egea E, Miller BJ, Kirkpatrick B

Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: A meta-analysis

Schizophrenia Research 2016; 174: 156-160

[View review abstract online](#)

Comparison	Prolactin levels in antipsychotic-naïve people with schizophrenia vs. controls.
Summary of evidence	Moderate quality evidence (small to medium-sized samples, inconsistent, precise, direct) suggests a large increase in prolactin levels in antipsychotic-naïve males and a medium-sized increase in antipsychotic-naïve females.
Prolactin	
<p><i>A significant, large effect of increased prolactin levels in males with schizophrenia and a medium-sized effect in females with schizophrenia;</i></p> <p>Males 7 studies, N = 332, $g = 1.02$, 95%CI, 0.77 to 1.26, $p < 0.001$, $I^2 = 81%$, $p < 0.001$ Females: 5 studies, N = 183, $g = 0.43$, 95%CI, 95%CI 0.11 to 0.76, $p < 0.01$, $I^2 = 66%$, $p < 0.02$ Meta-regression analyses showed no associations with the effect size and age, smoking, body mass index, year of publication, or cortisol levels. Authors report no evidence of publication bias.</p>	
Consistency	Inconsistent
Precision	Precise

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Directness	Direct
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Misiak B, Frydecka D, Loska O, Moustafa AA, Samochowiec J, Kasznia J, Stanczykiewicz B

Testosterone, DHEA and DHEA-S in patients with schizophrenia: A systematic review and meta-analysis

Psychoneuroendocrinology 2018; 89: 92-102

[View review abstract online](#)

Comparison	Testosterone, DHEA, and DHEA-S in people with schizophrenia vs. controls.
Summary of evidence	Moderate quality evidence (unclear sample size, inconsistent, some imprecision, direct) suggests a medium to large effect of elevated dehydroepiandrosterone – sulfate levels in people with schizophrenia. Testosterone levels were elevated only in first-episode psychosis patients and patients with an acute relapse.
Testosterone, DHEA, and DHEA-S	
<p><i>A significant, medium to large effect of elevated DHEA-S levels in people with schizophrenia;</i> 13 studies, N = unclear, $g = 0.75$, 95%CI 0.23 to 1.28, $p = 0.005$, $I^2 = 95\%$</p> <p><i>There were no significant differences in;</i></p> <p>Testosterone: 20 studies, N = unclear, $g = -0.04$, 95%CI -0.31 to 0.24, $p = 0.80$, $I^2 = 86\%$</p> <p>DHEA: 7 studies, N = unclear, $g = 0.02$, 95%CI -0.36 to 0.40, $p = 0.90$, $I^2 = 81\%$</p> <p>Subgroup analyses found people with first-episode psychosis had significantly higher levels of free testosterone ($g = 1.21$, $p = 0.009$) and DHEA-S ($g = 1.19$, $p < 0.001$) than controls. Acutely relapsed patients had higher levels of total testosterone ($g = 0.50$, $p < 0.001$). Total testosterone was elevated in stable multi-episode females ($g = 0.56$, $p < 0.001$) and reduced in stable multi-episode males ($g = -0.62$, $p = 0.006$).</p>	
Consistency	Inconsistent
Precision	Imprecise for DHEA-S, precise for testosterone and DHEA.
Directness	Direct

Misiak B, Bartoli F, Stramecki F, Samochowiec J, Lis M, Kasznia J, Jarosz K,

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Stanczykiewicz B

Appetite regulating hormones in first-episode psychosis: A systematic review and meta-analysis

Neuroscience and Biobehavioral Reviews 2019; 102: 362-70

[View review abstract online](#)

Comparison	Appetite regulating hormones in people with first-episode psychosis vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a small to medium-sized effect of higher insulin levels and a trend effect of lower leptin levels in people with first-episode psychosis. These effects were both significant in subgroup analyses of antipsychotic-naïve patients. The severity of negative symptoms was associated with increased effect size estimates for insulin.
Adiponectin, insulin, leptin, ghrelin, orexin, resistin, and visfatin	
<p><i>A small to medium-sized effect of higher insulin levels in first-episode psychosis patients;</i> 24 studies, N = 2,714, $g = 0.34$, 95%CI 0.19 to 0.49, $p < 0.001$, $I^2 = 70.5\%$</p> <p>This effect was similar in the subgroup analysis of antipsychotic-naïve patients. The severity of negative symptoms was associated with increased effect size estimates.</p> <p><i>There was a trend effect of lower levels of leptin in first-episode psychosis patients;</i> 10 studies, N = 845, $g = -0.33$, 95%CI -0.70 to 0.04, $p = 0.079$, $I^2 = 84\%$</p> <p>The effect was significant in the subgroup analysis of antipsychotic-naïve patients ($g = -0.62$, $p = 0.015$).</p> <p>Meta-regression showed no moderating effects of age, sex, BMI, study quality score, and the type of biological material (serum or plasma).</p> <p>There were no significant differences in levels of any other appetite regulating hormone.</p>	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Ragguett RM, Hahn M, Messina G, Chieffi S, Monda M, De Luca V

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Association between antipsychotic treatment and leptin levels across multiple psychiatric populations: An updated meta-analysis

Human Psychopharmacology 2017; 32: e2631

[View review abstract online](#)

Comparison	Pre-post treatment leptin levels in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a medium to large increase in leptin levels post treatment with antipsychotics, particularly olanzapine and clozapine.
Leptin	
<p><i>A significant, medium to large increase in leptin levels in people with schizophrenia;</i> 35 studies, N = 1,012, $g = 0.720$, 95%CI 0.442 to 0.998, $p \leq 0.001$</p> <p>Subgroup analyses of all patients (bipolar disorder and schizophrenia) showed olanzapine and clozapine produced more prominent increases in leptin levels than quetiapine and aripiprazole. Studies using enzyme-linked immunosorbent assay (ELISA) measures of leptin showed more prominent increases than studies using radioimmunoassay.</p>	
Consistency in results	Authors report results are inconsistent
Precision in results	Precise
Directness of results	Direct

Stubbs B, Wang AK, Vancampfort D, Miller BJ

Are leptin levels increased among people with schizophrenia versus controls? A systematic review and comparative meta-analysis

Psychoneuroendocrinology 2016; 63: 144-54

[View review abstract online](#)

Comparison	Leptin levels in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a small increase in leptin levels in people with schizophrenia compared to controls.

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Leptin	
<p><i>A small trend effect of increased leptin levels in people with schizophrenia;</i> 27 studies, N = 3,707, $g = 0.164$, 95%CI -0.014 to 0.341, $p = 0.07$, $I^2 = 83%$, $p < 0.01$ <i>The effect was significant with one outlier removed;</i> 26 studies, N = 3,687, $g = 0.196$, 95%CI 0.210 to 0.370, $p = 0.02$ Subgroup analysis found increased leptin levels in people with multi-episode schizophrenia ($g = 0.245$, $p = 0.01$), in females ($g = 0.557$, $p = 0.006$) and in people taking second generation antipsychotics ($g = 0.40$, $p = 0.001$) compared to controls. Meta-regression showed a lower percentage of males but not BMI moderated the results.</p>	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, d = Cohen's d and g = Hedges' g = standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect¹⁰.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if $RR > 2$ or < 0.5 and a large effect if $RR > 5$ or < 0.2 ¹¹. ORs and RRs are similar when the outcome is rare. InOR stands for logarithmic OR where a InOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence

limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed¹².

|| Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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