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The Promise of Biological Markers for Treatment Response in First-Episode Psychosis: A Systematic Review

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Successful treatment of first-episode psychosis is one of the major factors that impacts long-term prognosis. Currently, there are no satisfactory biological markers (biomarkers) to predict which patients with a first-episode psychosis will respond to which treatment. In addition, a non-negligible rate of patients does not respond to any treatment or may develop side effects that affect adherence to the treatments as well as negatively impact physical health. Thus, there clearly is a pressing need for defining biomarkers that may be helpful to predict response to treatment and sensitivity to side effects in first-episode psychosis. The present systematic review provides (1) trials that assessed biological markers associated with antipsychotic response or side effects in first-episode psychosis and (2) potential biomarkers associated with biological disturbances that may guide the choice of conventional treatments or the prescription of innovative treatments. Trials including first-episode psychoses are few in number. Most of the available data focused on pharmacogenetics markers with so far only preliminary results. To date, these studies yielded—beside markers for metabolism of antipsychotics—no or only a few biomarkers for response or side effects, none of which have been implemented in daily clinical practice. Other biomarkers exploring immunoinflammatory, oxidative, and hormonal disturbances emerged as biomarkers of first-episode psychoses in the last decades, and some of them have been associated with treatment response. In addition to pharmacogenetics, further efforts should focus on the association of emergent biomarkers with conventional treatments or with innovative therapies efficacy, where some preliminary data suggest promising results.

Key words: biomarker/first-episode psychosis/antipsychotic response/pharmacogenetic/inflammation/oxidative stress/hormonal/cortisol

Introduction

The current diagnostic criteria for psychotic disorders are based on self-report, behavioral observation, course criteria and lack substantial biological validation.[1,2] This contrasts sharply with several other areas of medicine where biological tests, based on validated biomarkers, aid in diagnostic and treatment decisions. Biological markers, or biomarkers, are measurements that quantify biological processes, disease state, or response to treatment. A biomarker of therapeutic response will be clinically useful only if it is accurate, reproducible, acceptable to the patient, easy to interpret, and has an adequate sensitivity and specificity.[3] Furthermore, ethical considerations in revealing likely diagnostic or course information to patients in a setting where such diagnoses may be stigmatized or therapeutic options limited. In psychiatry, biomarkers could improve diagnostic accuracy when added

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to clinical tools and could help the shift toward precision medicine, by providing tools to select treatment tailored to the individual.

This field of research is of particular importance in first-episode psychosis as inadequate or delayed treatment in the 2 or 3 first years of disease may lead to neuroanatomical and cognitive alterations, as well as worse functional outcome.[4] This reinforces the need for biomarkers that would improve early diagnosis and aid in use and personalization of effective treatments. Specifically, it is now well established that the prognosis of psychotic disorders is directly impacted by the duration of untreated psychosis[5–7] as well as by the adherence to treatment.[8,9] Prognosis of psychotic patients can be roughly divided into 3 categories: 25% of patients display a full response to treatment leading to a full recovery of a first episode, 50% of patients display recurrent illnesses with exacerbations and remissions, and the last 25% of the patients display an unfavorable course with incomplete response and recovery from the first psychosis.[10] Nonresponse or partial response to treatment is still common, especially for negative and cognitive symptoms, and nonresponsiveness is associated with longer hospitalization duration and poorer long-term outcome.[11] Compared with the general population, patients with a first-episode psychosis have a very high rate of all-cause (standardized mortality ratio [SMR] = 3.6), natural cause (SMR = 1.7), and un-natural cause (SMR = 13.3) mortality.[12]

Conversely, when treated early, patients with first-episode psychosis have a better response rate to pharmacological treatments compared with patients with a longer duration of illness.[9,13] This underlines a compelling rationale to develop a strategy for biomarker discovery and validation in first-episode psychotic patients.

The present article is not an exhaustive account of recent findings in biological research in psychosis. Instead, evidence reviewed in this article comprises a selective review of the literature, to highlight several potential promising biomarkers. Thus, we will (1) first systematically review monoamines biomarkers that were associated with treatment response and/or side effects in schizophrenia spectrum, nonaffective first-episode psychosis, and (2) second, describe other peripheral biomarkers such as immune inflammatory, oxidative stress, and hormonal biomarkers, which could open up new avenues for treatment response prediction in schizophrenia spectrum, nonaffective first-episode psychosis. We will present for each field of research a qualitative synthesis of biomarkers that were most robustly associated with first-episode psychosis, and if available, the potential treatments that may be indicated as adjunctive therapy in patients with disturbed biomarkers. Neuroimaging data was excluded because it is covered in a companion article.

Methods

The idea to find the "right" antipsychotic for the right patient is not new[14] and a number of studies have tried to identify biomarkers to better monitor and predict treatment response. Both peripheral amines and gene polymorphisms have been tested as potential biomarkers and are hereafter reported from systematic bibliographic searches employing Cochrane methodology. These were performed to find relevant English and non-English language trials from the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Medline Unindexed, EMBASE, PsycINFO, Google Scholar with each database being searched from inception to September 2014. The primary search strategy was "first episode psychosis" or "first episode schizophrenia" or "ultra high risk psychosis"; secondary research was then "response treatment" or "treatment side effect" as well as each potential biomarker that will be detailed below. Each common side effect (namely akathisia, dystonia, extrapyramidal syndrome, dyskinesia, weight gain, obesity) was also specifically explored. Only studies that assessed treatment response in first-episode psychosis by validated scales were included in the present work.

Results

Traditional Approaches: Hopes… and Disappointments

Peripheral Monoamines and Metabolites Blood or Urine Levels. Findings in studies of peripheral monoamines in first-episode psychosis come from elevated levels of plasma homovanillic acid (pHVA), the principal dopamine metabolite.[15] Elevated levels of pHVA before and during the first week of treatment were found to both predict response to first-generation antipsychotics (FGAs) drugs in first-episode psychosis.[16–18] This suggests that subjects who have the most disturbed dopaminergic transmission may be those who will better respond to antipsychotic drugs acting through D2 blockade, while nonresponders demonstrated increases in glutamate availability.[19–24] However, further replications of these findings are required because only 2 studies have been performed in first-episode psychosis, with limited sample sizes (less than 50 subjects in each study).

A similar significant association with elevated plasma levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (pMHPG) in first-episode psychosis was also reported in the same 2 studies,[16,17] but not in another one.[25]

A neurotoxic product of tryptophan metabolism, the (3-hydroxykynurenine [3-OHKY] quinolinic acid), was also found to predict severity of clinical symptoms during the first-episode psychosis.[26] Baseline levels of 3-OHKY in this study were also found to predict the

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degree of clinical improvement following brief treatment with antipsychotics.

Excess of serotonin release in first-episode psychosis, measured by a D-fenfluramine test, was found to be associated with FGAs nonresponse in one study.[27] No association between reduced serotonin in plasma and platelets prior to treatment and response to 5HT-blocking second-generation antipsychotics (SGAs) was found in patients with first-episode psychosis.[28] However, neocortical 5-HT2A binding in antipsychotic-naive first-episode patients was found to predict weight gain during antipsychotic treatment.[29] Among other markers of metabolic disturbances, signatures in urine, pregnanediol, citrate, and alpha-ketoglutarate were recently found to be significantly increased in first-episode psychosis, to be associated with the symptoms severity and were proposed as predictors of treatment response, but these results have not been replicated to date.[30]

Pharmacogenetic Studies. Less than 20 gene-targeted studies have explored association of candidate genes with treatment response in first-episode psychosis (tables 1 and 2).[31] As all antipsychotic drugs inhibit the dopamine D2 receptor, polymorphisms of the gene coding for this receptor were a plausible topic and have been studied most extensively, but the only 3 studies targeting 3 polymorphisms of the DRD2 gene (TaqIA, 241A>G, and 141Ins/Del) reported conflicting association results.[32–34] As clozapine, the most effective antipsychotic drug, blocks D4 receptors, and as some antipsychotics have a high anti-D3 activity, other dopaminergic receptor genes (encoding DRD1, DRD3, DRD4, and DRD5) were also studied, with largely negative results.[32,33,35] The catecholamine-O-methyl-transferase (COMT) gene was also not found to be associated with treatment response in first-episode psychosis,[36] although it has been found to modulate neural systems-level features linked to antipsychotic response.

Serotonin pathway-associated genes have also been studied, because SGA drugs were suggested to exert therapeutic activity by inhibiting serotonin receptors in addition to inhibiting dopaminergic receptors. Only one study explored the association between polymorphisms in all genes encoding serotonin receptors and treatment response in first-episode psychosis (5HT2A, 5HT2C, 5HT1A, 5HT1B, 5HT1D, 5HT6, and 5HT7) with negative results.[33] A negative association was further reported between the length polymorphism located in the serotonin transporter (5-HTT) gene promoter region and treatment response.[37] However, a significant association was found between the 5HT2C and the 5HT1A genes and improvement on negative symptoms.[32,38]

Signal transduction genes were also explored. A significant association was found between 2 of the single nucleotide polymorphisms (SNPs) of the gene coding for the signal transduction protein AKT1, and the same study found no significant association for GSK3ß.[33]

As antipsychotics are metabolized by cytochromes, cytochrome polymorphisms were explored too.[39] More specifically, the association between mutations that lead to cytochrome 2D6 (CYP2D6) inactivation and risperidone's effectiveness and tolerance in first-episode psychosis was explored in 2 studies with conflicting results: one found no association[40] and the other, with a smaller sample size (N = 35), found a significant lower response in patients with no functional CYP2D6 allele.[41]

Association between gene polymorphisms and treatment side effects were also explored. Antipsychotic-induced weight gain, which is the most common and severe side effect reported in first-episode psychosis treated with SGAs,[42] was reported to be associated with the 141 Ins/del polymorphism of the DRD2 gene[43] and with the 759C/T polymorphism of the 5HT2C gene.[44–46]

In conclusion of this first part, no peripheral monoamine markers or genetic predictors of antipsychotic response in first-episode psychosis have been discovered to date, which have entered clinical routine, despite intense research effort. No genome-wide association study (GWAS) is available so far for treatment response or side effects in first-episode psychosis although this is of course a target of pharmacogenomics studies in psychosis per se. There is therefore no evidence base, to date, to effectively predict which patient with a first-episode psychosis will respond to which treatment with genetic biomarkers. However, beyond the monoamine systems, other potential biomarkers of interest received increased attention in the recent decades.

Biomarkers of Immune Inflammation and Oxidative Stress

Immune inflammation is one of the major new avenues of research in psychotic disorders of the last decade. For each biological system, we will describe potential etiopathogenic mechanisms, the biomarkers that were the most robustly associated with first-episode psychosis, the association with antipsychotic response or side effects if available, and the potential innovative adjunctive treatments that may improve therapeutic response or side effects.

Cytokines as Biomarkers for Anti-inflammatory Treatments? Within the immune system, some of the key mediators are cytokines, which are small signaling molecules that can have a variety of downstream effects on both innate and adaptive immune systems. In first-episode psychosis, there have been a number of studies to report increased levels of cytokines including interleukin (IL)-1β, IL-6, IL-12, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, transforming growth factor-β, and sIL-2R levels,[47] and more recently IL-17, the complement protein C1Q activation, leukocyte

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Table 1. Studies of Biomarkers of Antipsychotic Response in the Treatment of First-Episode Psychosis (FEP)

Study	Antipsychotic	*N*	Population	Outcomes	Polymorphism	Major Findings
DRD2						
Reynolds et al[32]	Miscellaneous antipsychotic drugs[a]	117	FEP Chinese patients	Reduction in PANSS score	-TaqIA (rs1800497)	NS
Lencz et al[34]	Olanzapine (n = 28) Risperidone (n = 33)	61	FEP US patients	Clinical absence of delusions, hallucinations, or substantial thought disorder	−241A>G (rs1799978) −141 Ins/del (rs1799732)	Relative to wild-type homozygotes, G carriers (A−241G) exhibited a significantly faster time until response, whereas −141C Del carriers took a significantly longer time to respond. Diplotype analysis revealed similar results
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	−241A>G (rs1799978) −141 Ins/Del (rs1799732) -TaqIA (rs1800497)	Only Taq1A was significant predictor of treatment response to risperidone
DRD3						
Reynolds et al[32]	Miscellaneous antipsychotic drugs	117	FEP Chinese patients	Reduction in PANSS score	Ser9gly (rs6280)	The DRD3 genotype is associated with the change in total PANSS (P < .01), an effect reflecting positive and general (each P < .01) but not negative symptom improvement
DRD1						
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	DRD1: −1251Haelll (G>C) −800Haelll (C>T)	NS
DRD4						
Zalsman et al[35]	Risperidone	24	FEP Jewish adolescents	Change >40% in BPRS score	Exon III 48 bp repeat polymorphism	NS
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	DRD4: −120 bp duplication −616 G>C −521 T>C −48 bp repetition in exon III (S>L)	NS
DRD5						
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	DRD5: −1481 C>T	NS
5-HT2A						
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	HTR2A	NS
5-HT2C						
Reynolds et al[32]	Miscellaneous antipsychotic drugs	117	FEP Chinese patients	Reduction in PANSS score	HTR2C: −759C/T	The 5-HT2C promoter polymorphism was also associated with improvement in PANSS (P < .05), but reflecting effects on negative and general, but not positive, symptom scores

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Table 1. *Continued*

Study	Antipsychotic	*N*	Population	Outcomes	Polymorphism	Major Findings
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	HTR2C: −759 C>T −697C>G	NS
5-HT6						
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	HTR6: −267 C>T	NS
5-HT7						
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	HTR7: -SNP2 (rs3808932) -SNP5 (rs12412496)	NS
5-HT1A						
Reynolds et al[38]	Miscellanous antipsychotic drugs[b]	63	Spanish patients	Reduction in PANSS score and CDRS score	HTR1A: −1019 C>G	The polymorphism was associated with changes in negative and depressive symptoms but not positive symptoms
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	HTR1A: −1019 C>G	NS
5-HT1B/D						
Ikeda et al[33]	Risperidone	120	FEP Japanese patients	Reduction in PANSS score	HTR1B: −861 G>C HTR1D (rs674386)	NS
COMT						
Pelayo-Terán et al[36]	Risperidone (n = 60) Olanzapine (n = 55) Haloperidol (n = 54)	161	FEP Spanish patients	Reduction in YMRS, SAPS, SANS, HDRS scores	Val158Met	NS
AKT1						
Ikeda et al[33]	Risperidone	120	FEP	Reduction in PANSS score	AKT1: -SNP1 (rs3803300) -SNP2 (rs1130214) -SNP3 (rs3730358) -SNP4 (rs2498799) -SNP5 (rs2494732)	Two SNPs in AKT1 (AKT1-SNP1 [rs3803300] and AKT1-SNP5 [rs2494732]) were significant predictors of treatment response to risperidone
GSK3B						
Ikeda et al[33]	Risperidone	120	FEP	Reduction in PANSS score	GSK3B: -SNP6 (rs1574154) -SNP8 (rs2037547)	NS

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Table 1. *Continued*

Study	Antipsychotic	*N*	Population	Outcomes	Polymorphism	Major Findings
5-HTLLPR						
Vázquez-Bourgon et al[37]	Haloperidol (*n* = 45) Olanzapine (*n* = 52) Risperidone (*n* = 50)	147	FEP	Reduction in BPRS, SAPS, and SANS scores	−44 bp insertion/deletion in the promoter region -Functional polymorphism rs25531	No clear association was found between the rs25531 variant and treatment response. However, significant associations were observed between 5-HTT-LPR variants and early negative symptom response among first-episode patients with psychosis
Cytochrome (CYP2D6)						
Jovanović et al[40]	Risperidone	83	FEP	Reduction in PANSS score	CYP2D6 wild-type or mutation	NS
Barteček et al[41]	Risperidone	35	FEP	Reduction in PANSS score	CYP2D6 wild-type or mutation	Patients with CYP2D6 mutation showed a significantly lower reduction in psychotic symptoms and a greater severity of psychotic symptoms following risperidone treatment and higher doses of antipsychotics not metabolized by CYP2D6, which were used as comedication

Note: 5-HTT, serotonin transporter gene; BPRS, Brief Psychiatric Rating Scale; CDRS, Calgary Depression Rating Scale for Schizophrenia; COMT, catecholamine-O-methyl-transferase; DRD1-5, dopamine D1-5 receptor; HDRS, Hamilton Depression Rating Scale; L, long; NS, nonsignificant results; PANSS, Positive And Negative Symptoms Scale; S, short; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SNP, single nucleotide polymorphism; YMRS, Young Mania Rating Scale.
[a]Chlorpromazine (*n* = 66), risperidone (*n* = 43), clozapine (*n* = 4), fluphenazine (*n* = 3), sulpiride (*n* = 1), other antipsychotic drugs (*n* = 8).
[b]Olanzapine (*n* = 18), risperidone (*n* = 19), quetiapine (*n* = 10), haloperidol (*n* = 6), ziprasidone (*n* = 4), amisulpride (*n* = 1), no antipsychotic (*n* = 5).

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Table 2. Studies of Biomarkers of Side Effects in Antipsychotic Treatment for First-Episode Psychosis (FEP)

Side Effects				Outcomes		
DRD2						
Lencz et al[43]	Risperidone (n = 24) Olanzapine (n = 24)	58	FEP	Weight gain	−141C Ins/Del (rs1799732)	Deletion allele carriers demonstrated significantly more weight gain after 6 wk of treatment regardless of assigned medication
5-HT2C						
Reynolds et al[44]	Chlorpromazine (n = 69) Risperidone (n = 46) Clozapine (n = 4) Fluphenazine (n = 3) Sulpiride (n = 1)	123	FEP Chinese inpatients	Weight gain >7%	HTR2C: −759C/T	The −759T variant was associated with significantly less weight gain
Reynolds et al[45]	Clozapine	32	FEP Chinese patients	Increase in body mass index	HTR2C: −759C/T	The 10 patients with the −759T variant allele showed significantly less weight gain than those without this allele
Templeman et al[46]	Olanzapine + other antipsychotics	73	FEP Spanish Caucasian patients	Increase in body mass index	HTR2C: −759C/T	Patients with the −759T variant allele showed significantly less weight gain than those without this allele
Leptin gene						
Templeman et al[46]	Olanzapine + other antipsychotics	73	FEP Spanish Caucasian patients	Increase in body mass index	Leptin: −2548A/G	The -2548 leptin polymorphism was not associated with short-term (6 wk and 3 mo) weight increases but did show significant association with 9-mo antipsychotic-induced weight gain

Note: HTR2C, 5-hydroxytryptamine 2C receptor.

activation, and adiponectin.[48–51] Elevation of TNF-α is the most replicated finding in first-episode psychosis.[47,52] One study further suggested that biomarkers disturbances may be different between males and females with first-episode psychosis, suggesting that sex should be taken into account in future studies. In female patients, the inflammation-related analytes α1-antitrypsin, B-lymphocyte chemoattractant, and IL-15 showed negative associations with Positive And Negative Symptoms Scale score for schizophrenia (PANSS scores).[53]

Studying inflammatory biomarkers in untreated first-episode psychosis is relevant, as antipsychotic drugs are known to influence cytokine levels. Decreased levels of IL-1β and IFN-γ, and increased IL-12 and sIL-2R levels have been reported after antipsychotic administration.[54–56] However, few studies have so far assessed the association between cytokine levels and treatment response in first-episode psychoses: decreased IL-6 levels, increased levels of IL-10, and normalization of Th17 cells were all associated with positive treatment response.[52,57–59] However,

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the true variability in functional immune responsiveness assessed by the measures of cytokines is known to be a technical challenge that needs to be addressed.[60]

All these baseline immune-inflammatory disturbances may be biomarkers of interest for future anti-inflammatory add-on therapy.[61] The adjunction of celecoxib, a cyclooxygenase-2 inhibitor, to amisulpride in first-episode psychosis improved the clinical outcome as assessed by diminished PANSS positive, negative, and general subscores.[62] Unfortunately, no inflammatory biomarker that predicted response to celecoxib was reported at baseline in this study. Omega-3 fatty acids that were shown to have anti-inflammatory properties were also found to improve effectiveness and tolerance of antipsychotic drugs in first-episode psychosis, without identified baseline biomarker.[63] However, these studies await replication. Conflicting results were also found regarding the effectiveness of minocycline, a second-generation tetracycline that exhibited anti-inflammatory properties, when added to conventional antipsychotic treatments in early-phase schizophrenia.[64,65] Further studies are therefore warranted to determine which biomarker may be the most relevant one to orientate anti-inflammatory add-on therapies in first-episode psychoses.

Infectious Disease Markers for Specific Add-on Anti-infectious Therapies? Substantial research has supported prenatal exposure to infection as one of several established risk factor for subsequent risk for psychosis in the "maternal immune activation model."[66] In the Child Health and Development Study birth cohort, exposure to the influenza virus during pregnancy was associated with a 3-fold increased risk of schizophrenia among offspring[67] while serologically documented maternal exposure is related to a 5-fold greater risk of bipolar disorder with psychotic features.[68] Elevated IgG levels against *Toxoplasma gondii* was also associated with a 2-fold increased risk,[69] which was replicated in another cohort.[70] Herpes HSV-2 and rubella infections in mothers were also associated with increased risk of schizophrenia among offspring.[71,72] These observation data led to the hypothesis that pre- or perinatal infections may induce or modulate neurodevelopmental abnormalities, possibly through chronic central nervous system subclinical inflammation.

First-episode psychosis showed an increased prevalence of history of Toxoplasma infection compared with healthy controls (with an odd ratio around 2.7).[73] Bachmann et al[74] found that the levels of antibodies to *T. gondii* were associated with symptoms at admission and predictors of clinical outcome. It has been suggested that toxoplasmic serological status may predict effectiveness of psychotropic drug with antitoxoplasmic activity.[75–78] Recently, Wang et al[79] found that the administration of artemether, a strong antitoxoplasmic agent, was associated with greater reduction in the PANSS and the Clinical Global Impressions Scale scores at 8 weeks in toxoplasma-positive patients with first-episode psychosis. Further studies should determine if administering antipsychotic drugs with high antitoxoplasmic activity in toxopositive patients with first-episode psychosis may be associated with better response and outcome.

Higher IgG antibodies levels to cytomegalovirus in the cerebrospinal fluid (CSF),[80] higher HERV-W gag blood levels[81] were also identified in patients with first-episode psychosis compared with healthy controls but no significant association was observed between antibody levels and psychiatric measures in individuals positive for human herpes viruses in first-episode psychosis.[80,82]

These infections may act via a common pathway such as the cytokine response or a combination of pathways to elevate susceptibility to psychosis. In particular, gene–environment interactions are thought to account for the liability to psychosis and in this context, it is of major importance to note that genetic variants in the major histocompatibility complex recently reached genome-wide significance in several GWAS.[83–85] Some of these genes were also recently associated with haloperidol response.[86] These genes are critical to infections and inflammation responses. Hence, future studies of environmental factors such as infectious status should increase the likelihood of finding susceptible genes that lead to the description of relevant pathways to better understand first-episode psychosis.

Oxidative Stress Biomarkers for Antioxidant and/or Polyunsatured Fatty Acids Treatments? A considerable body of research has identified a compromised antioxidant defense in patients with first episode psychosis (for review see Fournier et al[87] and Yao et al [88]), that were associated with deterioration of school functioning from childhood to early adolescence,[89] gray matter loss,[90] and global cognition at baseline and at 2 years of follow-up.[91]

Superoxide dismutase, total antioxidant status, total glutathione, reduced glutathione, and catalase activity were nominated to be potential biomarkers of interest of oxidative stress disturbances in first-episode psychoses.[92–94] A genetic polymorphism of the D-aminoacid deoxide dismutase activator (DAOA/G72) gene, which relates to antioxidant pathways, was also associated with the transition to first-episode psychosis in high-risk adolescents.[95]

Oxidative stress was also linked to abnormal membrane polyunsatured fatty acids (PUFAs) metabolism in first-episode psychosis as well as in subjects at high risk for transition to psychosis. More specifically decreased arachidonic, docosahexaenoic, docosapentaenoic acids, phospholipase A2, and skin ceramide alterations were all found to be potential biomarkers of interest.[96–100] PUFAs levels correlated with negative symptoms after adjustment for potential confounders (ie, age, sex, and nicotine use)[101] and predicted myelin integrity in early-phase schizophrenia.[102]

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These studies reinforce the need to evaluate adjunctive antioxidant treatments in patients with oxidative disturbances to prevent a deteriorating course and development of the deficit syndrome.[103] A 12-week omega-3 supplementation reduced the transition rate to first-episode psychosis in an ultra-high-risk cohort[104] and was also associated with glutathione increase and improvement in negative symptoms in first-episode psychosis.[63,105] Oxidative neural injury may potentially be prevented by dietary PUFAs or antioxidants supplementation (eg, vitamins A, C, E, beta-carotene, Q enzyme, flavons, erythropoietin)[106,107] but randomized controlled trials are warranted to confirm this hypothesis.[108] It is to be expected that this line of research will be helped by the availability of positive emission tomography tracers for neuroinflammation that are applicable in practice.

Hormonal Biomarkers

Hormonal Stress Biomarkers Stress-Oriented Therapies?

Stress is known to play a key role in the development and course of many psychiatric disorders, including psychosis. Hypothalamo-pituitary-adrenal (HPA) axis function is often altered in the major psychiatric disorders and is an obvious focus for stage-based biomarker research. Cortisol is the primary hormone released by the HPA axis in response to stress and operates to maintain homeostasis of various physiological systems in the presence of increased external demand.[109] Dehydroepiandrosterone (DHEA) and its sulphated form (DHEAS) are major circulating corticosteroids that exert multiple effects on the central nervous system and have antistress and neuroprotective properties.[110] The concentration of DHEA in the blood fluctuates in parallel with cortisol in response to levels of adrenocorticotropin hormone, but without feedback control at the HPA level. DHEA/DHEAS concentrations increase during puberty reaching peak levels in young adulthood after which they markedly decline with age.[111] DHEA has potent antiglucocorticoid actions on the brain and can protect hippocampal neurons from glucocorticoid-induced neurotoxicity.[112,113] The corelease of DHEA in the acute stress response is thought to protect against the potentially damaging effects of excessive cortisol activity.

Multiple studies, but not all, found a basal overactivity of the HPA axis in male patients with first-episode psychosis that was, however, only inconsistently associated with disease severity.[114–117] HPA functioning was also found to be impaired in the ultra-high-risk stages of illness, with elevated cortisol levels indicating increased risk for transition, however, again with a low predictive power.[118,119] HPA disturbances may be maintained and worsened all along the illness progression[120] and correlated with severity of illness and aggressive behavior in male patients with first-episode psychosis.[121–126] Perceived stress significantly correlated with DHEAS and the cortisol/DHEAS ratio in controls, but not in patients with first-episode psychosis, possibly reflecting an impaired hormonal response to stress in patients with first-episode psychosis. Altogether, these results suggest that individuals with first-episode psychosis may develop a neurosteroid response to the first onset of psychosis, which may be associated with an increase of various adverse clinical features including aggression. Such a putative mechanism may become desensitized with the onset of chronic illness.[123]

Antipsychotics drugs were found to normalize diurnal cortisol hypersecretion but not the blunted cortisol awakening response in patients with first-episode psychosis.[116] Further studies are warranted to determine if HPA disturbances may be potential biomarkers for treatment response in first-episode psychosis.

Vasopressin/Oxytocin. Arginine-Vasopressin (AVP) is classically known for its role in the kidney as a potent antidiuretic hormone.[127] AVP is also released centrally during stressful experiences and is implicated in the regulation of the HPA axis, including cortisol secretion and in prosocial behavior.[128] Whereas oxytocin (OT) modulates trust, stress regulation, cardiovascular regulation, and under some conditions may have amnestic effects on verbal learning and memory, AVP is more typically associated with vigilance, increased reactivity to stressors, and improvements in verbal learning and memory.[129–133] Disruptions and interactions among these hormones may regulate physiology, behavior, and cognition allowing shifts between positive social behaviors and defensive states that are associated with the clinical symptoms of schizophrenia.

Rubin et al[134] found increased AVP levels in patients with first-episode psychosis compared with controls that were associated with greater positive symptoms and worse verbal learning in female, but not male patients. OT levels did not statistically differ between patients and controls and were unrelated to clinical symptoms or cognition in patients. In a further study, Rubin et al[135] found that AVP levels were also decreased in relatives of schizophrenia probands compared with controls, suggesting that AVP may be a biomarker of biological vulnerability for first-episode psychosis. Moreover, higher levels of OT were associated with better emotion recognition and general neuropsychological function in healthy controls as expected, but not in any proband or relative group. The dissociation of OT levels and behavioral function in all proband and relative groups suggested that risk and illness factors associated with psychotic disorders were not related to reduced OT levels but to a disruption in the ability of physiological levels of OT to modulate social cognition and neuropsychological function. These findings supported the role of neuroendocrine alterations in acute psychosis and the importance of examining sex-specific neuroendocrine alterations early in first-episode psychosis.

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Fasting Glycometabolism and Lipid Profile as Biomarkers for Weight Gain Under Treatment? Controversial results concerning insulin resistance and lipid metabolism have been reported in drug-free patients with first-episode psychosis: some studies reported higher insulin, higher insulin resistance, and higher C-peptide levels, and lower total cholesterol, high-density lipoprotein cholesterol, and apolipoprotein A1 levels in Spanish, Chinese, American patients with first-episode psychosis compared with healthy controls.[136–140] In one other recent study, the prolactin/IGF-1 and the insulin/IGF-1 ratios were found to be increased in female patients with a first-episode psychosis.[53] Only one study conducted in the Canadian population found negative results.[141] Direct measurements of CSF glucose levels further found a significant increase in glucose levels and decrease in acetate and lactate concentrations in drug-naive patients with early schizophrenia compared with matched healthy controls.[142] In a recent Chinese study, the FokI SNP was found to possibly contribute to the disturbance of glucose–insulin homeostasis in patients with first-episode psychosis and to increase the susceptibility to the risperidone-induced insulin resistance.[143] It is still unclear to date whether these markers may be used to prevent treatment-induced weight gain in patients with first-episode psychosis and further efforts are warranted. Among other potential treatments of patients with glucose/insulin abnormalities, metformin was found to be effective in weight gain and insulin resistance prevention of patients with first-episode psychosis treated with olanzapine and may be of particular interest in patients with baseline glycometabolism disturbances.[144]

Conclusion

To date there are no biomarkers which confidently predict the response to treatment or the side effects in patients with first-episode psychosis. Several limits may explain this lack of findings. First, identifying biomarkers that would help unravel different etiologies and pathophysiological mechanisms would enable to conduct clinical trials in specific subtypes of psychosis using more reliable predictive biomarkers of treatment response. Second, up to now, most studies are limited to the evaluation of the statistical association between a specific biomarker and a subscore of the PANSS (for positive, negative, or general psychopathology symptomatology). It may be suggested that more accurate assessments of symptom changes may help to identify biomarkers. In the PANSS, positive and negative subscores may include symptoms that may correspond to different pathophysiological mechanisms with different biomarkers. It can be hypothesized that biomarkers of treatment response in hallucinations may differ from delusions or aggressiveness for example. Moreover, cognitive symptoms were not assessed by specific neuropsychological tests in these studies, which may help to identify specific biomarkers too. Third, many antipsychotics were used in the same study (mostly haloperidol, olanzapine, risperidone, and clozapine) but these antipsychotics have different affinities for monoaminergic receptors and thus may probably have different efficacy biomarkers. In the fourth place, baseline symptoms severity was not taken into account in the analyses. These limits may explain the lack of reliable biomarker identified up to now. Therefore, our teams created a European Consortium to optimize the treatment response in patients with first episode of psychosis. We thus develop the OPTiMiSE trial (http://www.optimisetrial.eu), the largest follow-up study on subjects with first-episode psychosis, in which 500 individuals are treated with atypical antipsychotics. Each patient is clinically evaluated intensively and blood samples are collected at baseline, and after 4, 10, and 22 weeks of treatment, to extract DNA, RNA, plasma, and serum. These samples will be analyzed with a combination of genomic, metabolomic, and proteomic approaches with the aims of discovering blood-based biomarkers with predictive power for efficacy of treatment.

This review of the literature showed multiple possible paths in the development of personalized medicine based on biological markers. Immunoinflammatory hypotheses provided the largest bundle of biomarkers that may indicate the need for innovative early add-on therapies with a better benefit/risk profile than conventional treatments, namely polyunsatured fatty acids, vitamins, anti-inflammatory drugs, antioxidants, or minocycline.

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References

1. Insel TR, Voon V, Nye JS, et al. Innovative solutions to novel drug development in mental health. *Neurosci Biobehav Rev*. 2013;37:2438–2444.
2. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry*. 2012;17:1174–1179.
3. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circulation*. 2006;113:2335–2362.
4. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl*. 1998;172:53–59.
5. Chiliza B, Asmal L, Emsley R. Early intervention in schizophrenia in developing countries: focus on duration of untreated psychosis and remission as a treatment goal. *Int Rev Psychiatry*. 2012;24:483–488.
6. Drancourt N, Etain B, Lajnef M, et al. Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. *Acta Psychiatr Scand*. 2013;127:136–144.
7. Fraguas D, Merchán-Naranjo J, del Rey-Mejías Á, et al. A longitudinal study on the relationship between duration of untreated psychosis and executive function in early-onset first-episode psychosis. *Schizophr Res*. 2014;158:126–133.
8. Subotnik KL, Ventura J, Gretchen-Doorly D, et al. The impact of second-generation antipsychotic adherence on positive and negative symptoms in recent-onset schizophrenia. *Schizophr Res*. 2014;159:95–100.
9. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry*. 2003;160:1396–1404.
10. Lieberman JA. Prediction of outcome in first-episode schizophrenia. *J Clin Psychiatry*. 1993;54(suppl):13–17.
11. Capdevielle D, Norton J, Jaussent I, et al. Extended duration of hospitalization in first episode psychosis: an evaluation of its clinical justification. *Psychiatry Res*. 2013;209:160–166.
12. Reininghaus U, Dutta R, Dazzan P, et al. Mortality in schizophrenia and other psychoses: a 10-year follow-up of the SOP first-episode cohort [published online ahead of print September 27, 2014]. *Schizophr Bull*. doi: 10.1093/schbul/sbu138.
13. Kahn RS, Sommer IE. The neurobiology and treatment of first-episode schizophrenia [published online ahead of print July 22, 2014]. *Mol Psychiatry*. doi: 10.1038/mp.2014.66.
14. Tansella M, Balestrieri A. The choice of neuroleptics in the treatment of schizophrenia: a critical review. *Arzneimittelforschung*. 1976;26:943–945.
15. Luykx JJ, Bakker SC, Lentjes E, et al. Genome-wide association study of monoamine metabolite levels in human cerebrospinal fluid. *Mol Psychiatry*. 2014;19:228–234.
16. Nagaoka S, Iwamoto N, Arai H. First-episode neuroleptic-free schizophrenics: concentrations of monoamines and their metabolites in plasma and their correlations with clinical responses to haloperidol treatment. *Biol Psychiatry*. 1997;41:857–864.
17. Koreen AR, Lieberman J, Alvir J, et al. Plasma homovanillic acid levels in first-episode schizophrenia. Psychopathology and treatment response. *Arch Gen Psychiatry*. 1994;51:132–138.
18. Baeza I, Castro-Fornieles J, Deulofeu R, et al. Plasma homovanillic acid differences in clinical subgroups of first episode schizophrenic patients. *Psychiatry Res*. 2009;168:110–118.
19. Howes OD, Kapur S. A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). *Br J Psychiatry*. 2014;205:1–3.
20. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry*. 2012;69:776–786.
21. Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. *Curr Pharm Des*. 2009;15:2550–2559.
22. Egerton A, Brugger S, Raffin M, et al. Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. *Neuropsychopharmacology*. 2012;37:2515–2521.
23. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry*. 2012;169:1203–1210.
24. Demjaha A, Egerton A, Murray RM, et al. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biol Psychiatry*. 2014;75:e11–e13.
25. Yoshimura R, Ueda N, Shinkai K, Nakamura J. Plasma levels of homovanillic acid and the response to risperidone in first episode untreated acute schizophrenia. *Int Clin Psychopharmacol*. 2003;18:107–111.
26. Condray R, Dougherty GG Jr, Keshavan MS, et al. 3-Hydroxykynurenine and clinical symptoms in first-episode neuroleptic-naive patients with schizophrenia. *Int J Neuropsychopharmacol*. 2011;14:756–767.
27. Mohr P, Horácek J, Motlová L, Libiger J, Czobor P. Prolactin response to D-fenfluramine challenge test as a predictor of treatment response to haloperidol in acute schizophrenia. *Schizophr Res*. 1998;30:91–99.
28. van der Heijden FM, Tuinier S, Fekkes D, Sijben AE, Kahn RS, Verhoeven WM. Atypical antipsychotics and the relevance of glutamate and serotonin. *Eur Neuropsychopharmacol*. 2004;14:259–265.
29. Rasmussen H, Ebdrup BH, Oranje B, Pinborg LH, Knudsen GM, Glenthøj B. Neocortical serotonin2A receptor binding predicts quetiapine associated weight gain in antipsychotic-naive first-episode schizophrenia patients. *Int J Neuropsychopharmacol*. 2014;17:1729–1736.
30. Cai HL, Li HD, Yan XZ, et al. Metabolomic analysis of biochemical changes in the plasma and urine of first-episode neuroleptic-naïve schizophrenia patients after treatment with risperidone. *J Proteome Res*. 2012;11:4338–4350.

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31. Brandl EJ, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotics. *Can J Psychiatry*. 2014;59:76–88.
32. Reynolds GP, Yao Z, Zhang X, Sun J, Zhang Z. Pharmacogenetics of treatment in first-episode schizophrenia: D3 and 5-HT2C receptor polymorphisms separately associate with positive and negative symptom response. *Eur Neuropsychopharmacol*. 2005;15:143–151.
33. Ikeda M, Yamanouchi Y, Kinoshita Y, et al. Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. *Pharmacogenomics*. 2008;9:1437–1443.
34. Lencz T, Robinson DG, Xu K, et al. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. *Am J Psychiatry*. 2006;163:529–531.
35. Zalsman G, Frisch A, Lev-Ran S, et al. DRD4 exon III polymorphism and response to risperidone in Israeli adolescents with schizophrenia: a pilot pharmacogenetic study. *Eur Neuropsychopharmacol*. 2003;13:183–185.
36. Pelayo-Terán JM, Pérez-Iglesias R, Vázquez-Bourgon J, et al. Catechol-O-methyltransferase Val158Met polymorphism and negative symptoms after acute antipsychotic treatment in first-episode non-affective psychosis. *Psychiatry Res*. 2011;185:286–289.
37. Vázquez-Bourgon J, Arranz MJ, Mata I, et al. Serotonin transporter polymorphisms and early response to antipsychotic treatment in first episode of psychosis. *Psychiatry Res*. 2010;175:189–194.
38. Reynolds GP, Arranz B, Templeman LA, Fertuzinhos S, San L. Effect of 5-HT1A receptor gene polymorphism on negative and depressive symptom response to antipsychotic treatment of drug-naive psychotic patients. *Am J Psychiatry*. 2006;163:1826–1829.
39. Ravyn D, Ravyn V, Lowney R, Nasrallah HA. CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence. *Schizophr Res*. 2013;149:1–14.
40. Jovanović N, Božina N, Lovrić M, Medved V, Jakovljević M, Peleš AM. The role of CYP2D6 and ABCB1 pharmacogenetics in drug-naïve patients with first-episode schizophrenia treated with risperidone. *Eur J Clin Pharmacol*. 2010;66:1109–1117.
41. Barteček R, Juřica J, Zrůstová J, Kašpárek T, Pindurová E, Žourková A. Relevance of CYP2D6 variability in first-episode schizophrenia patients treated with risperidone. *Neuro Endocrinol Lett*. 2012;33:236–244.
42. Zhang JP, Malhotra AK. Pharmacogenetics of antipsychotics: recent progress and methodological issues. *Expert Opin Drug Metab Toxicol*. 2013;9:183–191.
43. Lencz T, Robinson DG, Napolitano B, et al. DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia. *Pharmacogenet Genomics*. 2010;20:569–572.
44. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. *Lancet*. 2002;359:2086–2087.
45. Reynolds GP, Zhang Z, Zhang X. Polymorphism of the promoter region of the serotonin 5-HT(2C) receptor gene and clozapine-induced weight gain. *Am J Psychiatry*. 2003;160:677–679.
46. Templeman LA, Reynolds GP, Arranz B, San L. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. *Pharmacogenet Genomics*. 2005;15:195–200.
47. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*. 2011;70:663–671.
48. Song X, Fan X, Song X, et al. Elevated levels of adiponectin and other cytokines in drug naïve, first episode schizophrenia patients with normal weight. *Schizophr Res*. 2013;150:269–273.
49. Severance EG, Gressitt KL, Halling M, et al. Complement C1q formation of immune complexes with milk caseins and wheat glutens in schizophrenia. *Neurobiol Dis*. 2012;48:447–453.
50. Borovcanin M, Jovanovic I, Radosavljevic G, et al. Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. *J Psychiatr Res*. 2012;46:1421–1426.
51. Di Nicola M, Cattaneo A, Hepgul N, et al. Serum and gene expression profile of cytokines in first-episode psychosis. *Brain Behav Immun*. 2013;31:90–95.
52. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. *Schizophr Res*. 2014;155:101–108.
53. Ramsey JM, Schwarz E, Guest PC, et al. Distinct molecular phenotypes in male and female schizophrenia patients. *PLoS One*. 2013;8:e78729.
54. Tourjman V, Kouassi É, Koué MÈ, et al. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. *Schizophr Res*. 2013;151:43–47.
55. Crespo-Facorro B, Pérez-Iglesias R, Mata I, et al. Long-term (3-year) effectiveness of haloperidol, risperidone and olanzapine: results of a randomized, flexible-dose, open-label comparison in first-episode nonaffective psychosis. *Psychopharmacology (Berl)*. 2012;219:225–233.
56. MacDowell KS, García-Bueno B, Madrigal JL, et al. Risperidone normalizes increased inflammatory parameters and restores anti-inflammatory pathways in a model of neuroinflammation. *Int J Neuropsychopharmacol*. 2013;16:121–135.
57. Kubistova A, Horacek J, Novak T. Increased interleukin-6 and tumor necrosis factor alpha in first episode schizophrenia patients versus healthy controls. *Psychiatr Danub*. 2012;24(suppl 1):S153–S156.
58. de Witte L, Tomasik J, Schwarz E, et al. Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment. *Schizophr Res*. 2014;154:23–29.
59. Ding M, Song X, Zhao J, et al. Activation of Th17 cells in drug naïve, first episode schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;51:78–82.
60. Duffy D, Rouilly V, Libri V, et al. Functional analysis via standardized whole-blood stimulation systems defines the boundaries of a healthy immune response to complex stimuli. *Immunity*. 2014;40:436–450.
61. Fond G, Hamdani N, Kapczinski F, et al. Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. *Acta Psychiatr Scand*. 2014;129:163–179.
62. Müller N, Krause D, Dehning S, et al. Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. *Schizophr Res*. 2010;121:118–124.
63. Berger GE, Proffitt TM, McConchie M, et al. Ethyl-eicosapentaenoic acid in first-episode psychosis: a

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randomized, placebo-controlled trial. *J Clin Psychiatry*. 2007;68:1867–1875.

64. Liu F, Guo X, Wu R, et al. Minocycline supplementation for treatment of negative symptoms in early-phase schizophrenia: a double blind, randomized, controlled trial. *Schizophr Res*. 2014;153:169–176.
65. Levkovitz Y, Mendlovich S, Riwkes S, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry*. 2010;71:138–149.
66. Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Dev Neurobiol*. 2012;72:1272–1276.
67. Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004;61:774–780.
68. Canetta SE, Bao Y, Co MD, et al. Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring. *Am J Psychiatry*. 2014;171:557–563.
69. Brown AS, Schaefer CA, Quesenberry CP Jr, Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry*. 2005;162:767–773.
70. Mortensen PB, Nørgaard-Pedersen B, Waltoft BL, Sørensen TL, Hougaard D, Yolken RH. Early infections of Toxoplasma gondii and the later development of schizophrenia. *Schizophr Bull*. 2007;33:741–744.
71. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry*. 2001;58:1032–1037.
72. Mortensen PB, Pedersen CB, Hougaard DM, et al. A Danish National Birth Cohort study of maternal HSV-2 antibodies as a risk factor for schizophrenia in their offspring. *Schizophr Res*. 2010;122:257–263.
73. Torrey EF, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. *Schizophr Bull*. 2012;38:642–647.
74. Bachmann S, Schröder J, Bottmer C, Torrey EF, Yolken RH. Psychopathology in first-episode schizophrenia and antibodies to Toxoplasma gondii. *Psychopathology*. 2005;38:87–90.
75. Strobl JS, Cassell M, Mitchell SM, Reilly CM, Lindsay DS. Scriptaid and suberoylanilide hydroxamic acid are histone deacetylase inhibitors with potent anti-Toxoplasma gondii activity in vitro. *J Parasitol*. 2007;93:694–700.
76. Jones-Brando L, Torrey EF, Yolken R. Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of Toxoplasma gondii. *Schizophr Res*. 2003;62:237–244.
77. Goodwin DG, Strobl JS, Lindsay DS. Evaluation of five antischizophrenic agents against Toxoplasma gondii in human cell cultures. *J Parasitol*. 2011;97:148–151.
78. Fond G, Macgregor A, Tamouza R, et al. Comparative analysis of anti-toxoplasmic activity of antipsychotic drugs and valproate. *Eur Arch Psychiatry Clin Neurosci*. 2014;264:179–183.
79. Wang HL, Xiang YT, Li QY, et al. The effect of artemether on psychotic symptoms and cognitive impairment in first-episode, antipsychotic drug-naive persons with schizophrenia seropositive to Toxoplasma gondii. *J Psychiatr Res*. 2014;53:119–124.
80. Leweke FM, Gerth CW, Koethe D, et al. Antibodies to infectious agents in individuals with recent onset schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2004;254:4–8.
81. Yao Y, Schröder J, Nellåker C, et al. Elevated levels of human endogenous retrovirus-W transcripts in blood cells from patients with first episode schizophrenia. *Genes Brain Behav*. 2008;7:103–112.
82. Amminger GP, McGorry PD, Berger GE, et al. Antibodies to infectious agents in individuals at ultra-high risk for psychosis. *Biol Psychiatry*. 2007;61:1215–1217.
83. Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk of schizophrenia. *Nature*. 2009;460:744–747.
84. Shi J, Levinson DF, Duan J, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature*. 2009;460:753–757.
85. Purcell SM, Wray NR, Stone JL, et al.; International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748–752.
86. Drago A, Giegling I, Schäfer M, et al. Genome-wide association study supports the role of the immunological system and of the neurodevelopmental processes in response to haloperidol treatment. *Pharmacogenet Genomics*. 2014;24:314–319.
87. Fournier M, Ferrari C, Baumann PS, et al. Impaired metabolic reactivity to oxidative stress in early psychosis patients. *Schizophr Bull*. 2014;40:973–983.
88. Yao JK, Dougherty GG, Reddy RD, Matson WR, Kaddurah-Daouk R, Keshavan MS. Associations between purine metabolites and monoamine neurotransmitters in first-episode psychosis. *Front Cell Neurosci*. 2013;7:90.
89. Mukherjee B, Ghosh S, Chatterjee M. Chemopreventive efficacy of selenomethionine and its role in the antioxidant defense system in 2-acetylaminofluorene-induced hepatocarcinogenesis in rats. *J Exp Ther Oncol*. 1996;1:209–217.
90. Fraguas D, Gonzalez-Pinto A, Micó JA, et al. Decreased glutathione levels predict loss of brain volume in children and adolescents with first-episode psychosis in a two-year longitudinal study. *Schizophr Res*. 2012;137:58–65.
91. Martínez-Cengotitabengoa M, Micó JA, Arango C, et al. Basal low antioxidant capacity correlates with cognitive deficits in early onset psychosis. A 2-year follow-up study. *Schizophr Res*. 2014;156:23–29.
92. Micó JA, Rojas-Corrales MO, Gibert-Rahola J, et al. Reduced antioxidant defense in early onset first-episode psychosis: a case-control study. *BMC Psychiatry*. 2011;11:26.
93. Reddy R, Keshavan M, Yao JK. Reduced plasma antioxidants in first-episode patients with schizophrenia. *Schizophr Res*. 2003;62:205–212.
94. Raffa M, Atig F, Mhalla A, Kerkeni A, Mechri A. Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients. *BMC Psychiatry*. 2011;11:124.
95. Mössner R, Schuhmacher A, Wagner M, et al. DAOA/G72 predicts the progression of prodromal syndromes to first episode psychosis. *Eur Arch Psychiatry Clin Neurosci*. 2010;260:209–215.
96. Reddy RD, Keshavan MS, Yao JK. Reduced red blood cell membrane essential polyunsaturated fatty acids in first episode schizophrenia at neuroleptic-naive baseline. *Schizophr Bull*. 2004;30:901–911.
97. Kale A, Naphade N, Sapkale S, et al. Reduced folic acid, vitamin B12 and docosahexaenoic acid and increased homocysteine and cortisol in never-medicated schizophrenia patients: implications for altered one-carbon metabolism. *Psychiatry Res*. 2010;175:47–53.

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98. Smesny S, Schmelzer CE, Hinder A, et al. Skin ceramide alterations in first-episode schizophrenia indicate abnormal sphingolipid metabolism. *Schizophr Bull*. 2013;39:933–941.
99. Smesny S, Milleit B, Hipler UC, et al. Omega-3 fatty acid supplementation changes intracellular phospholipase A2 activity and membrane fatty acid profiles in individuals at ultra-high risk for psychosis. *Mol Psychiatry*. 2014;19:317–324.
100. Khan MM, Evans DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. *Schizophr Res*. 2002;58:1–10.
101. Amminger GP, McGorry PD. Update on ω-3 polyunsaturated fatty acids in early-stage psychotic disorders. *Neuropsychopharmacology*. 2012;37:309–310.
102. Peters BD, Machielsen MW, Hoen WP, et al. Polyunsaturated fatty acid concentration predicts myelin integrity in early-phase psychosis. *Schizophr Bull*. 2013;39:830–838.
103. Mahadik SP, Mukherjee S, Scheffer R, Correnti EE, Mahadik JS. Elevated plasma lipid peroxides at the onset of nonaffective psychosis. *Biol Psychiatry*. 1998;43:674–679.
104. Amminger GP, Schäfer MR, Papageorgiou K, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2010;67:146–154.
105. Wood SJ, Cocchi L, Proffitt TM, et al. Neuroprotective effects of ethyl-eicosapentaenoic acid in first episode psychosis: a longitudinal T2 relaxometry pilot study. *Psychiatry Res*. 2010;182:180–182.
106. Fond G, Macgregor A, Attal J, et al. Treating patients with schizophrenia deficit with erythropoietin? *Psychiatry Clin Neurosci*. 2012;66:375–382.
107. Sivrioglu EY, Kirli S, Sipahioglu D, Gursoy B, Sarandöl E. The impact of omega-3 fatty acids, vitamins E and C supplementation on treatment outcome and side effects in schizophrenia patients treated with haloperidol: an open-label pilot study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:1493–1499.
108. Okusaga OO. Accelerated aging in schizophrenia patients: the potential role of oxidative stress. *Aging Dis*. 2014;5:256–262.
109. Peters A, Conrad M, Hubold C, Schweiger U, Fischer B, Fehm HL. The principle of homeostasis in the hypothalamus-pituitary-adrenal system: new insight from positive feedback. *Am J Physiol Regul Integr Comp Physiol*. 2007;293:R83–R98.
110. Wolkowitz OM, Epel ES, Reus VI. Stress hormone-related psychopathology: pathophysiological and treatment implications. *World J Biol Psychiatry*. 2001;2:115–143.
111. Morley JE, Kaiser F, Raum WJ, et al. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. *Proc Natl Acad Sci USA*. 1997;94:7537–7542.
112. Kimonides VG, Spillantini MG, Sofroniew MV, Fawcett JW, Herbert J. Dehydroepiandrosterone antagonizes the neurotoxic effects of corticosterone and translocation of stress-activated protein kinase 3 in hippocampal primary cultures. *Neuroscience*. 1999;89:429–436.
113. Kimonides VG, Khatibi NH, Svendsen CN, Sofroniew MV, Herbert J. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity. *Proc Natl Acad Sci USA*. 1998;95:1852–1857.
114. Walsh P, Spelman L, Sharifi N, Thakore JH. Male patients with paranoid schizophrenia have greater ACTH and cortisol secretion in response to metoclopramide-induced AVP release. *Psychoneuroendocrinology*. 2005;30:431–437.
115. Mondelli V, Pariante CM, Navari S, et al. Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis. *Schizophr Res*. 2010;119:75–78.
116. Mondelli V, Dazzan P, Hepgul N, et al. Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: the role of stress and of antipsychotic treatment. *Schizophr Res*. 2010;116:234–242.
117. Ryan MC, Sharifi N, Condren R, Thakore JH. Evidence of basal pituitary-adrenal overactivity in first episode, drug naïve patients with schizophrenia. *Psychoneuroendocrinology*. 2004;29:1065–1070.
118. Walker EF, Trotman HD, Pearce BD, et al. Cortisol levels and risk for psychosis: initial findings from the North American prodrome longitudinal study. *Biol Psychiatry*. 2013;74:410–417.
119. Cullen AE, Zunszain PA, Dickson H, et al. Cortisol awakening response and diurnal cortisol among children at elevated risk for schizophrenia: relationship to psychosocial stress and cognition. *Psychoneuroendocrinology*. 2014;46:1–13.
120. Girshkin L, Matheson SL, Shepherd AM, Green MJ. Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. *Psychoneuroendocrinology*. 2014;49:187–206.
121. Aas M, Dazzan P, Mondelli V, et al. Abnormal cortisol awakening response predicts worse cognitive function in patients with first-episode psychosis. *Psychol Med*. 2011;41:463–476.
122. Garner B, Phassouliotis C, Phillips LJ, et al. Cortisol and dehydroepiandrosterone-sulphate levels correlate with symptom severity in first-episode psychosis. *J Psychiatr Res*. 2011;45:249–255.
123. Beyazyüz M, Albayrak Y, Beyazyüz E, Unsal C, Göka E. Increased serum dehydroepiandrosterone sulfate in the first episode but not in subsequent episodes in male patients with schizophrenia. *Neuropsychiatr Dis Treat*. 2014;10:687–693.
124. Strous RD, Maayan R, Kaminsky M, Blumensohn R, Weizman A, Spivak B. DHEA and DHEA-S levels in hospitalized adolescents with first-episode schizophrenia and conduct disorder: a comparison study. *Eur Neuropsychopharmacol*. 2009;19:499–503.
125. Strous RD, Maayan R, Lapidus R, et al. Increased circulatory dehydroepiandrosterone and dehydroepiandrosterone-sulphate in first-episode schizophrenia: relationship to gender, aggression and symptomatology. *Schizophr Res*. 2004;71:427–434.
126. Oades RD, Schepker R. Serum gonadal steroid hormones in young schizophrenic patients. *Psychoneuroendocrinology*. 1994;19:373–385.
127. Weitzman RE, Kleeman CR. The clinical physiology of water metabolism. Part I: The physiologic regulation of arginine vasopressin secretion and thirst. *West J Med*. 1979;131:373–400.
128. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci*. 2011;12:524–538.
129. Strupp B, Weingartner H, Goodwin FK, Gold PW. Neurohypophyseal hormones and cognition. *Pharmacol Ther*. 1983;23:267–279.
130. Carter CS. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology*. 1998;23:779–818.

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131. Heinrichs M, Domes G. Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans. *Prog Brain Res*. 2008;170:337–350.
132. Gutkowska J, Jankowski M. Oxytocin revisited: its role in cardiovascular regulation. *J Neuroendocrinol*. 2012;24:599–608.
133. Ferris CF. Functional magnetic resonance imaging and the neurobiology of vasopressin and oxytocin. *Prog Brain Res*. 2008;170:305–320.
134. Rubin LH, Carter CS, Bishop JR, et al. Peripheral vasopressin but not oxytocin relates to severity of acute psychosis in women with acutely-ill untreated first-episode psychosis. *Schizophr Res*. 2013;146:138–143.
135. Rubin LH, Carter CS, Bishop JR, et al. Reduced levels of vasopressin and reduced behavioral modulation of oxytocin in psychotic disorders. *Schizophr Bull*. 2014;40:1374–1384.
136. Wu X, Huang Z, Wu R, et al. The comparison of glycometabolism parameters and lipid profiles between drug-naïve, first-episode schizophrenia patients and healthy controls. *Schizophr Res*. 2013;150:157–162.
137. Verma SK, Subramaniam M, Liew A, Poon LY. Metabolic risk factors in drug-naive patients with first-episode psychosis. *J Clin Psychiatry*. 2009;70:997–1000.
138. Verma S, Liew A, Subramaniam M, Poon LY. Effect of treatment on weight gain and metabolic abnormalities in patients with first-episode psychosis. *Aust N Z J Psychiatry*. 2009;43:812–817.
139. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry*. 2003;160:284–289.
140. Arranz B, Rosel P, Ramírez N, et al. Insulin resistance and increased leptin concentrations in noncompliant schizophrenia patients but not in antipsychotic-naive first-episode schizophrenia patients. *J Clin Psychiatry*. 2004;65:1335–1342.
141. Sengupta S, Parrilla-Escobar MA, Klink R, et al. Are metabolic indices different between drug-naïve first-episode psychosis patients and healthy controls? *Schizophr Res*. 2008;102:329–336.
142. Holmes E, Tsang TM, Huang JT, et al. Metabolic profiling of CSF: evidence that early intervention may impact on disease progression and outcome in schizophrenia. *PLoS Med*. 2006;3:e327.
143. Jiang P, Zhu MQ, Li HD, Liu YP, Cai HL, Zhang LM. Effects of vitamin D receptor polymorphisms on the risk of schizophrenia and metabolic changes caused by risperidone treatment. *Psychiatry Res*. 2014;215:806–807.
144. Wu TH, Chiu CC, Shen WW, et al. Pharmacokinetics of olanzapine in Chinese male schizophrenic patients with various smoking behaviors. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1889–1893.

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