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

Guillaume Fond1–3, Marc-Antoine d’Albis1–3, Stéphane Jamain1–3, Ryad Tamouza4, Celso Arango5, W. Wolfgang Fleischhacker6, Birte Glenthøj7, Markus Leweke6, Shôn Lewis9, Phillip McGuire10, Andreas Meyer-Lindenberg8, Iris E. Sommer11, Inge Winter-van Rossum11, Shitij Kapur12, René S. Kahn11, Dan Rujescu13, and Marion Leboyer1–3

1INSERM U955, Eq 15 Psychiatrie Génétique et psychopathologie, Créteil, France; 2Université Paris Est-Créteil, DHU Pe-PSY, Pôle de Psychiatrie des Hôpitaux Universitaires H Mondor, Créteil, France; 3Fondation FondaMental, Créteil, France; 4Jean Dausset Laboratory & INSERM, UMRS 940, Hôpital Saint Louis, Paris, France; 5Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, ISG, School of Medicine, Universidad Complutense, CIBERSAM, Madrid, Spain; 6Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria; 7Center for Neuropsychiatric Schizophrenia Research & Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Psychiatric Hospital Center Glostrup, University of Copenhagen, Faculty of Health and Medical Sciences, Denmark; 8Central Institute of Mental Health, University of Heidelberg/Medical Faculty Mannheim, Mannheim, Germany; 9Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK; 10Department of Psychosis Studies, Institute of Psychiatry, King’s College London, London, UK; 11Department of Psychiatry, Brain Center Rudolf Magnus, UMC Utrecht, Utrecht, The Netherlands; 12Institute of Psychiatry, King’s College London, London, UK; 13Department of Psychiatry, University of Halle, Halle, Germany

To whom correspondence should be addressed; Pole de Psychiatrie et d’addictologie, Hôpital A. Chenevier, 40 rue de Mesly, Créteil F-94010, France; tel: 33-1-78-68-23-72, fax: 33-1-78-68-23-81, e-mail: guillaume.fond@gmail.com

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, 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
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. 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 as well as by the adherence to treatment. 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. 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. 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.

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. 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 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. 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. 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. 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, but not in another one.

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. Baseline levels of 3-OHKY in this study were also found to predict the
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. 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. However, neocortical 5-HT2A binding in antipsychotic-naive first-episode patients was found to predict weight gain during antipsychotic treatment. 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.

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). 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 poly- morphisms of the DRD2 gene (Taq1A, 241A>G, and 141Ins/Del) reported conflicting association results. 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. The catecholamine-O-methyl-transferase (COMT) gene was also not found to be associated with treatment response in first-episode psychosis, 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. A negative association was further reported between the length polymorphism located in the serotonin transporter (5-HTT) gene promoter region and treatment response. However, a significant association was found between the 5HT2C and the 5HT1A genes and improvement on negative symptoms.

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 GSK3β.

As antipsychotics are metabolized by cytochromes, cytochrome polymorphisms were explored too. 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 and the other, with a smaller sample size (N = 35), found a significant lower response in patients with no functional CYP2D6 allele.

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, was reported to be associated with the 141Ins/del polymorphism of the DRD2 gene and with the 759C/T polymorphism of the 5HT2C gene.

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 and more recently IL-17, the complement protein C1Q activation, leukocyte
<table>
<thead>
<tr>
<th>Study</th>
<th>Antipsychotic</th>
<th>N</th>
<th>Population</th>
<th>Outcomes</th>
<th>Polymorphism</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD2</td>
<td>Miscellaneous antipsychotic drugs</td>
<td>117</td>
<td>FEP Chinese patients</td>
<td>Reduction in PANSS score</td>
<td>TaqIA (rs1800497)</td>
<td>NS</td>
</tr>
<tr>
<td>Reynolds et al</td>
<td>Olanzapine (n = 28) Risperidone (n = 33)</td>
<td>61</td>
<td>FEP US patients</td>
<td>Clinical absence of delusions, hallucinations, or substantial thought disorder</td>
<td>-241A&gt;G (rs1799978) -141 Ins/del (rs1799732)</td>
<td>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. Diplo</td>
</tr>
<tr>
<td>Ikeda et al</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>Ser9gly (rs6280)</td>
<td>Only TaqIA was significant predictor of treatment response to risperidone</td>
</tr>
<tr>
<td>DRD3</td>
<td>Miscellaneous antipsychotic drugs</td>
<td>117</td>
<td>FEP Chinese patients</td>
<td>Reduction in PANSS score</td>
<td>DRD3: −1251 Haelll (G&gt;C) −800 Haelll (C&gt;T)</td>
<td>The DRD3 genotype is associated with the change in total PANSS (P &lt; .01), an effect reflecting positive and general (each P &lt; .01) but not negative symptom improvement</td>
</tr>
<tr>
<td>Ikeda et al</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>DRD5: −1481 C&gt;T</td>
<td>NS</td>
</tr>
<tr>
<td>Zalsman et al</td>
<td>Risperidone</td>
<td>24</td>
<td>FEP Jewish adolescents</td>
<td>Change &gt;40% in BPRS score</td>
<td>Exon III 48 bp repeat polymorphism</td>
<td>NS</td>
</tr>
<tr>
<td>Ikeda et al</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR2A</td>
<td>NS</td>
</tr>
<tr>
<td>Ikeda et al</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR2C: −759 C&gt;T</td>
<td>The 5-HT2C promoter polymorphism was also associated with improvement in PANSS (P &lt; .05), but reflecting effects on negative and general, but not positive, symptom scores</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Antipsychotic</th>
<th>N</th>
<th>Population</th>
<th>Outcomes</th>
<th>Polymorphism</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikeda et al[33]</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR2C: −759 C&gt;T, −697C&gt;G</td>
<td>NS</td>
</tr>
<tr>
<td>5-HT6</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR6: −267 C&gt;T</td>
<td>NS</td>
</tr>
<tr>
<td>5-HT7</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR7: −267 C&gt;T</td>
<td>NS</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR1A: −1019 C&gt;G</td>
<td>The polymorphism was associated with changes in negative and depressive symptoms but not positive symptoms NS</td>
</tr>
<tr>
<td>Reynolds et al[38]</td>
<td>Miscellaneously antipsychotic drugs</td>
<td>63</td>
<td>FEP Spanish patients</td>
<td>Reduction in PANSS score and CDRS score</td>
<td>HTR1A: −1019 C&gt;G</td>
<td></td>
</tr>
<tr>
<td>Ikeda et al[33]</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR1A: −1019 C&gt;G</td>
<td></td>
</tr>
<tr>
<td>5-HT1B/D</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP Japanese patients</td>
<td>Reduction in PANSS score</td>
<td>HTR1B: −861 G&gt;C, HTR1D (rs674386)</td>
<td>NS</td>
</tr>
<tr>
<td>COMT</td>
<td>Risperidone</td>
<td>161</td>
<td>FEP Spanish patients</td>
<td>Reduction in YMRS, SAPS, SANS, HDRS scores</td>
<td>Val158Met</td>
<td>NS</td>
</tr>
<tr>
<td>Pelayo-Terán et al[8]</td>
<td>Risperidone</td>
<td>161</td>
<td>FEP Spanish patients</td>
<td>Reduction in YMRS, SAPS, SANS, HDRS scores</td>
<td>Val158Met</td>
<td></td>
</tr>
<tr>
<td>AKT1</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP</td>
<td>Reduction in PANSS score</td>
<td>AKT1: SNP1 (rs3803300), SNP2 (rs1130214), SNP3 (rs3730358), SNP4 (rs2497999), SNP5 (rs2494732)</td>
<td>Two SNPs in AKT1 (AKT1-SNP1 [rs3803300] and AKT1-SNP5 [rs2494732]) were significant predictors of treatment response to risperidone</td>
</tr>
<tr>
<td>GSK3B</td>
<td>Risperidone</td>
<td>120</td>
<td>FEP</td>
<td>Reduction in PANSS score</td>
<td>GSK3B: SNP6 (rs1574154), SNP8 (rs2037547)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Antipsychotic</th>
<th>N</th>
<th>Population</th>
<th>Outcomes</th>
<th>Polymorphism</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HTTLPR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Vázquez-Bourgon et al 37</td>
<td>Haloperidol (n = 45)</td>
<td></td>
<td>FEP</td>
<td>Reduction in BPRS, SAPS, and SANS scores</td>
<td>−44 bp insertion/deletion in the promoter region -Functional polymorphism rs25531</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olanzapine (n = 52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risperidone (n = 50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytochrome (CYP2D6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Jovanović et al 40</td>
<td>Risperidone</td>
<td>83</td>
<td>FEP</td>
<td>Reduction in PANSS score</td>
<td>CYP2D6 wild-type or mutation</td>
<td>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</td>
</tr>
<tr>
<td>Barteček et al 41</td>
<td>Risperidone</td>
<td>35</td>
<td>FEP</td>
<td>Reduction in PANSS score</td>
<td>CYP2D6 wild-type or mutation</td>
<td></td>
</tr>
</tbody>
</table>

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.

*Chlorpromazine (n = 66), risperidone (n = 43), clozapine (n = 4), fluphenazine (n = 3), sulpiride (n = 1), other antipsychotic drugs (n = 8).

*Olanzapine (n = 18), risperidone (n = 19), quetiapine (n = 10), haloperidol (n = 6), ziprasidone (n = 4), amisulpride (n = 1), no antipsychotic (n = 5).
Table 2. Studies of Biomarkers of Side Effects in Antipsychotic Treatment for First-Episode Psychosis (FEP)

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Outcomes</th>
<th>Outcomes</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lencz et al 43</td>
<td>Risperidone (n = 24)</td>
<td>58</td>
<td>FEP</td>
</tr>
<tr>
<td></td>
<td>Olanzapine (n = 24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT2C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reynolds et al 44</td>
<td>Chlorpromazine (n = 69)</td>
<td>123</td>
<td>FEP Chinese inpatients</td>
</tr>
<tr>
<td></td>
<td>Risperidone (n = 46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clozapine (n = 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluphenazine (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sulpiride (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reynolds et al 45</td>
<td>32</td>
<td>FEP Chinese patients</td>
<td>Increase in body mass index</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Templeman et al 46</td>
<td>Olanzapine + other antipsychotics</td>
<td>73</td>
<td>FEP Spanish Caucasian patients</td>
</tr>
<tr>
<td>Leptin gene</td>
<td>Templeman et al 46</td>
<td>Olanzapine + other antipsychotics</td>
<td>73</td>
</tr>
</tbody>
</table>

Note: HTR2C, 5-hydroxytryptamine 2C receptor.

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,
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 addition 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-inflammatory 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 offspring67 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 al64 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 al79 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 toxoplasma 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 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.81,82 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 Polyunsaturated 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 al87 and Yao et al88), 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 polyunsaturated 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
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. A 12-week omega-3 supplementation reduced the transition rate to first-episode psychosis in an ultra-high-risk cohort and was also associated with glutathione increase and improvement in negative symptoms in first-episode psychosis. Oxidative neural injury may potentially be prevented by dietary PUFAs or antioxidants supplementation (eg, vitamins A, C, E, beta-carotene, Q enzyme, flavons, erythropoietin) but randomized controlled trials are warranted to confirm this hypothesis.

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. 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. 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. DHEA has potent antiglucocorticoid actions on the brain and can protect hippocampal neurons from glucocorticoid-induced neurotoxicity. 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. 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. HPA disturbances may be maintained and worsened all along the illness progression and correlated with severity of illness and aggressive behavior in male patients with first-episode psychosis. 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.

Antipsychotics drugs were found to normalize diurnal cortisol hypersecretion but not the blunted cortisol awakening response in patients with first-episode psychosis. 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 diuretic hormone. 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. 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. 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 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 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.
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. 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. Only one study conducted in the Canadian population found negative results. 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. 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. 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.

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 polyunsaturated fatty acids, vitamins, anti-inflammatory drugs, antioxidants, or minocycline.

Funding

European Commission within the 7th Program (HEALTH-F2-2010-242114); INSERM (Institut National de la Santé et de la Recherche Médicale); AP-HP (Assistance Publique des Hôpitaux de Paris); Fondation Fonamental (RTRS Santé Mentale); Investissements d’Avenir program managed by the ANR under reference (ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01).

Acknowledgments

We express all our thanks to the patients who participated in the studies included in the present review.

Dr C.A. has been a consultant to or has received honoraria or grants from Abbot, AMGEN, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Instituto de Salud Carlos III, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier, Shire, Takeda, and Schering Plough.

B.G. is the leader of a Lundbeck Foundation Center of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), which is partially financed by an independent grant from the Lundbeck Foundation based on international review and partially...
financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. She has nothing else to declare.

Dr R.S.K. has been on DSMB’s for Janssen, Otsuka, Roche, and Sunovion.

Dr M.L. has received speaker and research grants from Otsuka, Janssen Cilag, Roche, and Sunovion.

Dr W.W Fleishhacker has received speaker, consultant fees from Roche and Eli Lilly.

Dr A.M.-L. has received speaker and consultant fees partially funded by Sanofi and Roche.

Dr M.L. has received speaker fees from Servier and is the Region of Denmark, the University of Copenhagen, and financed by the Mental Health Services in the Capital Region of Denmark.

References


