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A systematic review of metabolite biomarkers of schizophrenia

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ABSTRACT

Current diagnosis of schizophrenia relies exclusively on the potentially subjective interpretation of clinical symptoms and social functioning as more objective biological measurement and medical diagnostic tests are not presently available. The use of metabolomics in the discovery of disease biomarkers has grown in recent years. Metabolomic methods could aid in the discovery of diagnostic biomarkers of schizophrenia. This systematic review focuses on biofluid metabolites associated with schizophrenia. A systematic search of Web of Science and Ovid Medline databases was conducted and 63 studies investigating metabolite biomarkers of schizophrenia were included. A review of these studies revealed several potential metabolite signatures of schizophrenia including reduced levels of essential polyunsaturated fatty acids (EPUFAs), vitamin E and creatinine; and elevated levels of lipid peroxidation metabolites and glutamate. Further research is needed to validate these biomarkers and would benefit from large cohort studies and more homogeneous and well-defined subject groups.

1. Introduction

Schizophrenia is a debilitating mental disorder with lifetime prevalence rates of between 0.3% and 0.7% (American Psychiatric Association, 2013). It is characterised by positive symptoms including delusions, hallucinations, disorganised speech and catatonic behaviour; and negative symptoms such as avolition (lack of motivation) and emotional withdrawal (American Psychiatric Association, 2013). Symptoms usually appear in adolescence or early adulthood and it is important to identify individuals affected at the earliest stages of the disorder (Focking et al., 2016; Gaebel and Zielasek, 2015; Perkins et al., 2005). Currently, the diagnosis of schizophrenia relies solely on the somewhat subjective interpretation of clinical symptoms presented by patients (Chan et al., 2015; Cheniaux et al., 2009). In addition, several disorders for e.g. bipolar disorder and autism share some of the symptomology of schizophrenia and this can also lead to difficulty in providing the correct diagnosis (Quinones and Kaddurah-Daouk, 2009). Early diagnosis is important, with evidence suggesting that early identification and treatment of subjects with psychotic illness significantly improves their clinical outcome (Larsen et al., 2011). Clinical characteristics alone are of limited predictive value and therefore biological predictors of schizophrenia and of the psychosis prodrome will be of enormous value (Cannon et al., 2016; Chan et al., 2015; Weickert et al., 2013).

The interest in identifying biomarkers of schizophrenia and other psychotic disorders has rapidly grown in recent years (Lai et al., 2016; Money and Bousman, 2013; Pickard, 2015). Biomarkers of these disorders could contribute to a more objective and reliable diagnosis and help to overcome some of the problems which exist with current purely clinical diagnostic methods. Furthermore, there is the potential that such biomarkers could also help in the identification of individuals at risk of developing psychotic disorders among those in the at-risk mental state (ARMS) (Hurlemann et al., 2008; Stojanovic et al., 2014) or at ultra-high risk for psychosis (UHR) (McNamara et al., 2016; Santoro et al., 2015), provide a method of diagnosis at an early stage (Sethi and Brietzke, 2015), or help predict treatment response or measures of disease outcome. In recent years, "-omics" methods have been applied in the search for biomarkers of schizophrenia and other diseases. These methods include genomics, transcriptomics, proteomics and the more recent field of metabolomics (Money and Bousman, 2013; Quinones and Kaddurah-Daouk, 2009; Sethi and Brietzke, 2015). Some recent findings of potential schizophrenia/psychosis biomarkers using "-omics" methods include elevated *MBP* and *NDEL1* gene expression in early psychosis patients (Gouvea et al., 2016) and elevated baseline levels of certain cytokines in ARMS patients who transitioned to psychotic disorder (Focking et al., 2016; Hayes et al., 2014; Sabherwal et al., 2016). The present review focuses on metabolomics which is the measurement of small molecules present in biological samples (e.g. tissue, blood, urine, cerebrospinal fluid). Together the metabolites in a sample comprise the metabolome. Metabolomics gives an instantaneous snapshot of the physiological status of the organism at a certain time (Peng et al., 2015) and unless samples are analysed prior to disease onset the metabolic alterations will reflect changes following disease onset. Traditional methods of measuring metabolite biomarkers were hypothesis driven and focused on assaying single metabolites however, current metabolomics techniques are capable of quantifying

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hundreds of metabolites at one time allowing an explorative approach into investigating biomarkers of disease along with hypothesis driven approaches (Quinones and Kaddurah-Daouk, 2009).

Methods commonly used include mass spectrometry (MS) coupled with gas chromatography (GC), liquid chromatography (LC) or capillary electrophoresis (CE); and nuclear magnetic resonance (NMR) spectroscopy (Quinones and Kaddurah-Daouk, 2009; Zhang et al., 2012). These techniques each have their strengths and weaknesses and at present there is no single analytical platform capable of detecting all metabolites present in the metabolome. Therefore an integrated approach using more than one platform is often adopted in modern studies to provide the most sensitive and reliable measurements (Zhang et al., 2012).

Although biomarker research has greatly advanced in recent years, no robust biomarkers of schizophrenia or psychotic disorders generally have yet been identified (Pickard, 2015; Prata et al., 2014). This systematic review summarises previous research into the metabolomics of schizophrenia, looking at both modern metabolomics techniques along with classical methods used in earlier studies, to reveal any potential biomarkers. The review will focus on studies investigating metabolite differences between schizophrenia subjects and control subjects and also look at how metabolite levels relate to symptom severity in patients.

2. Methods

This systematic review was conducted in accordance with PRISMA guidelines (Moher et al., 2009). Articles were identified by searching for titles in the Ovid Medline and Web of Science (WoS) databases using the following search terms: "(schizophreni? OR psychosis OR "at risk mental state" OR "at-risk mental state" OR ARMS OR "ultra-high risk" OR UHR) AND (metabolom* OR metabolite? OR lipidom* OR lipid? OR biomarker? OR "biological marker?" OR "biological signature?") NOT (rat? or animal?)". The search was restricted to English language journal articles with human subjects, published between January 1970 and June 2016.

The searches returned 538 records after duplicates were removed. 67 records reached inclusion criteria after screening of abstracts. Two of these did not have an accessible full text version leaving 65 full text articles to review. Two studies were discarded after a review of the full text due to not providing enough statistical or methodological information leaving 63 articles to be included in the review (Fig. 1).

Abstracts from the search records were screened using the following criteria for inclusion/exclusion: Only experimental published papers were included; reviews and meta-analyses were excluded. Papers were included if they measured any biofluid metabolite levels in humans with schizophrenia, schizophrenia spectrum disorders or at risk of developing schizophrenia (e.g. At-risk mental state (ARMS) subjects and those with a family history of the disorder) AND: a) compared subjects to a healthy control group or other psychiatric disorder/psychosis patient group; OR b) measured the relationship between metabolite levels and symptom severity (measured using a reliable measurement scale e.g. brief psychiatric rating scale (BPRS), positive and negative symptoms scale (PANSS), scale for the assessment of positive symptoms (SAPS), scale for the assessment of negative symptoms (SANS)) AND; c) NOT solely focused on the effects of antipsychotic medications on metabolite levels; d) NOT focused on unrelated variables e.g. comparing patients with Tardive Dyskinesia and those without; or those who have attempted suicide and those who have not; e) NOT focused on metabolites measured in brain tissue.

3. Results

63 articles met search criteria and were included in this review (Fig. 1). Significant findings relating to metabolites in schizophrenia patients have been summarised in Tables 1–5. Results are divided into sections based on metabolite classes which are as follows: (1) lipids and lipid-like molecules including fatty acids, steroids and other lipid-like molecules; (2) carbohydrate metabolism, organic acids and derivatives; and (3) other metabolites. Results include metabolites where significantly different levels have been reported in schizophrenia or psychosis

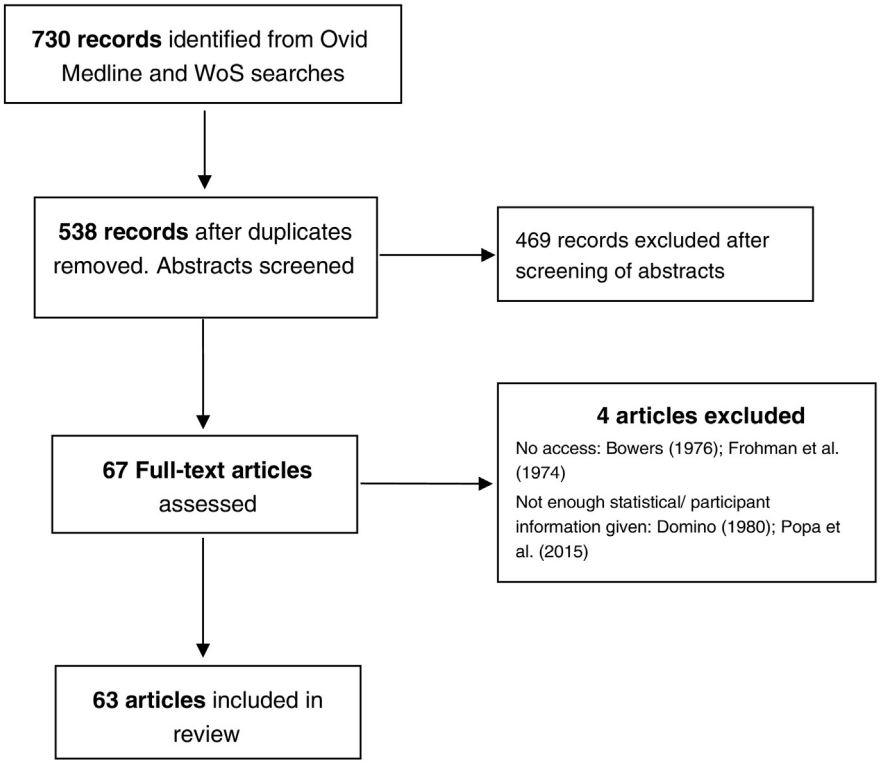

Fig. 1. Flow chart of selection process. WoS: Web of Science.

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