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Metabolomics Biomarkers for Precision Psychiatry

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Abstract

The treatment of psychiatric disorders remains a significant challenge in part due to imprecise diagnostic criteria and incomplete understanding of the molecular pathology involved. Current diagnostic and pharmacological treatment guidelines use a uniform approach to address each disorder even though psychiatric clinical presentation and prognosis within a disorder are known to be heterogeneous. Limited therapeutic success highlights the need for a precision medicine approach in psychiatry, termed precision psychiatry. To practice precision psychiatry, it is essential to research and develop multiple omics-based biomarkers that consider environmental factors and careful phenotype determination. Metabolomics, which lies at the endpoint of the "omics cascade," allows for detection of alterations in systems-level metabolites within biological pathways, thereby providing insights into the mechanisms that underlie various physiological conditions and pathologies. The eicosanoids, a family of metabolites derived from oxygenated polyunsaturated fatty acids, play a key role in inflammatory mechanisms and have been implicated in psychiatric disorders such as anorexia nervosa and depression. This review (1) provides background on the current clinical challenges of psychiatric disorders, (2) gives an overview of metabolomics application as a tool to develop improved biomarkers for precision psychiatry, and (3) summarizes current knowledge on metabolomics and lipidomic findings in common psychiatric disorders, with a focus on eicosanoids. Metabolomics is a promising tool for precision psychiatry. This research has great potential for both discovering biomarkers and elucidating molecular mechanisms underlying psychiatric disorders.

Keywords

Systematic review; Psychiatric disorders; Metabolomics; Eicosanoids; Polyunsaturated fatty acids; Biomarkers

10.1 Challenges in Clinical Psychiatry

Psychiatric disorders can impair one's thinking, perceptions, emotions, and behaviors, resulting in significant distress or impairment of personal functioning [1]. The five most common categories of psychiatric disorders are *anxiety disorders*, including generalized anxiety disorder and post-traumatic stress disorder; *mood disorders*, such as depression and bipolar disorder; *schizophrenia and psychotic disorders*; *dementia*; and *eating disorders*, including anorexia nervosa and binge-eating disorder. Psychiatric disorders are prevalent,

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with an astonishing 46.4% lifetime prevalence of having at least one major psychiatric disorders in the United States [2]. Psychiatric conditions represent a major public health problem due to their associated disabilities [3] and mortality [4]. The estimated global burden of psychiatric disorders accounts for up to 32% of years lived with disability, and more than 13% of disability-adjusted life-years [5]. Moreover, psychiatric disorders are significant predictors of the onset and severity of subsequent serious medical illnesses such as heart disease [6].

Diagnosis in psychiatry is based on a classification system that includes clinical nosologies such as the International Classification of Diseases [7] and the Diagnostic and Statistical Manual of Mental Disorders [8]. The current diagnostic system is universally applied, not only clinically, but also in research and policy settings such as drug-approval and insurance-reimbursement systems. Although these diagnostic criteria are regularly revised to improve validity, more disagreements about diagnosis fundamentals are found in psychiatry than in any other branch of medicine [9, 10]. The heterogeneous presentation of psychiatric disorders is a result not only of phenotypic, biological, and genetic heterogeneity, but also the outcome of complex interactions between environmental and biological factors. A lack of clear understanding about the complex psychopathology contributing to each disorder leads to inadequate or ineffective treatment strategy. Taking depression as an example, although antidepressants provide substantial benefits for many, issues including lack of efficacy, intolerance, delayed therapeutic onset, and risk of relapse are frequently reported. In fact, results from one of the largest randomized trials involving 4041 patients from 41 clinical sites around the country showed that the remission rate from the first line of treatment was only 28% [11]. Clearly, there is a lot of room for improvement in clinical psychiatry.

10.2 Omics-Based Strategies in Precision Psychiatry

A promising strategy to overcome obstacles in clinical psychiatry is “precision medicine,” an emerging approach that aims to improve health and advance individualized care by taking into account “each person’s variability in genes, environment, and lifestyle” [12]. This ambitious initiative requires collecting dense data from a large number of cohort studies, including studies of psychiatric disorders [13]. The rise of biotechnologies that simultaneously measure thousands of data points has been timely in meeting the needs of precision medicine. These high-throughput technologies yield multifaceted data, including genomics, epigenomics, transcriptomics, proteomics, metabolomics and are collectively referred to as “multi-omics” [14]. Used effectively, multi-omics investigation enables exploration of complex interactions in biological systems and their roles in health and disorders.

Among individual “omics” disciplines, the most frequently published in psychiatry are genome-wide association studies (GWAS) [15, 16]. GWAS have revealed evidence of substantial pleiotropy or shared genetic etiology among several psychiatric disorders [17]. Due to the polygenic, multi-factorial nature of psychiatric disorders and the inherent limitations of GWAS design, the genetic loci identified are typically small in effect size and of questionable clinical significance [18]. By itself, GWAS likely remain limited in yielding

significant translational advances to improve diagnostic accuracy and treatment effectiveness [19].

A multidisciplinary approach that combines multiple omics data– integrated multi-dimensional omics– is much more likely to offer complementary vantage points to enrich our knowledge of expression and functions of genomic factors associated with a disorder, thus improving diagnosis, prognosis, and treatment development [20]. For example, a recent GWAS meta-analysis revealed a high degree of correlation [average genetic correlation (rg) = 0.40] among bipolar disorder, major depressive disorder (MDD), and schizophrenia [21]. On the other hand, a molecular profiling approach characterizing 181 proteins and small molecules in serum showed excellent potential to distinguish schizophrenia from healthy controls, as well as from subjects with MDD, bipolar disorder, and Asperger syndrome [22]. Studies incorporating both investigation methods in the same study cohort likely will lead to significant improvement in diagnostic accuracy.

Biomarkers are *objective* surrogates of genetic, tissue-specific, and environmental factors, as well as their interactions [23]. An effective biomarker system such as integrated multi-dimensional omics will thus serve as one of the most informative research and clinical tools and move the practice of psychiatry closer to the goal of precision psychiatry [24].

10.3 Unique Role of Metabolomics Biomarkers

While GWAS provide information on genomic risk factors that are often unmodifiable, metabolomics studies measure our metabolic state, determined not only by genomic factors but also modified by diet, environmental factors, and host factors such as the childhood experiences and gut microbiome. The metabolic profile serves as a quantifiable, dynamic readout of biochemical state that can inform underlying molecular mechanisms of the disorder or phenotype. As such, metabolomics data have higher relevance to the “disordered state” and may serve well as predictive, prognostic, diagnostic biomarkers [25] for psychiatric disorders. The remainder of this chapter provides a brief summary of the analytical techniques most commonly used in metabolomics studies, and reports on and discusses a selection of psychiatric metabolomics and lipidomic studies. In particular, it highlights a specific class of metabolites called eicosanoids and their unique role in unraveling how disorders are influenced by the interactive relationship between genes and diet [26].

10.4 Overview of Metabolomics Analytical Techniques and Methodologies

The likelihood of success for precision psychiatry lies in the accuracy and comprehensive dimensionality of the data. Analytical techniques for metabolomics have come a long way. Nuclear magnetic resonance (NMR), mass spectrometry (MS), and electrochemical detection are commonly used techniques to identify and quantify metabolites [27]. NMR is less sensitive than MS-based methods, yet it is favorable due to the absence of detection bias and is useful in identifying novel metabolite structures [28]. Compared to NMR, MS is superior in mass analysis capabilities and is usually used together with other separation instruments such as gas chromatography (GC), liquid chromatography (LC), or capillary

electrophoresis (CE). GC and LC have traditionally been used in metabolomics studies; CE has gained popularity in recent years [27]. In clinical laboratories, liquid chromatography-tandem mass spectrometry (LC-MS/MS) is known for high specificity and sensitivity [29]. LC-MS/MS can detect compounds with low molecular weight (such as eicosanoids) with better sensitivity, selectivity, and higher throughput than high performance liquid chromatography or GC-MS [29].

Equally as important as choosing the right instrument for metabolomics measurement are the design and analysis aspects of metabolomics. Metabolomics analysis methods can broadly be categorized in two ways. “Untargeted metabolomics” (global) analysis captures a wide array of detectable metabolites, including those with unknown functions or that have not been seen previously [30]. Untargeted metabolomics offers the unique advantage of discovering novel perturbations and detecting the relationship between interconnected metabolites from multiple pathways in an unbiased fashion [30]. In contrast, a “targeted metabolomics” approach focuses on a narrower, pre-specified cluster of metabolites that have been hypothesized to play a role in the disorder studied. Internal standards allow for quantification of analytes in targeted metabolomics, offering better control of sensitivity, stability, and reproducibility of each targeted metabolite. Having some prior knowledge of these metabolites and biochemical pathways means associations identified in targeted analysis can move more quickly to other molecular or translational studies to further define mechanisms underlying the phenotype associations.

Recent advances in these complementary approaches have helped elucidate informative metabolomics biomarkers relevant in psychiatric disorders such as eicosanoids with inflammation regulatory functions. These biomarkers show promise for capturing early biochemical changes in the disease state [31] and enabling early diagnosis of psychiatric disorders. While analytical considerations for generating metabolomics data are beyond the scope of this chapter, it is important to note that metabolites are volatile, with a short half-life, making rigorous quality control of biological samples and assay preparation necessary to ensure validity of the findings.

10.5 Metabolomics Studies of Common Psychiatric Disorders

Using an untargeted metabolomics approach and proton NMR (1H-NMR) system, a serum metabolite profile was effective in separating schizophrenia from healthy controls [32]. Moreover, the results seem to reinforce the importance of the glycolysis pathway and a “hyperglutamate hypothesis” previously proposed [33] in schizophrenia. Examining both serum and urinary metabolites, 1H-NMR and gas chromatography with two-dimensional gas chromatography (GC-TOFMS) platforms revealed several pathways implicated in schizophrenia including fatty acid metabolism, carbohydrate metabolism, and amino acid metabolism [34].

Metabolic profiles of cerebrospinal fluid samples from drug-naïve (or minimally treated) first-onset schizophrenia and controls suggest brain-specific alterations in glucoregulatory processes were intrinsic to disease because these dysregulations normalized after treatment with atypical antipsychotic medications in half of schizophrenia patients [35]. Patients with

schizophrenia and other psychiatric disorders often experience significant weight gain during their course of treatment [36]. Lipidomic and metabolomic analyses have identified lipids associated with medication-associated weight gain [37] and metabolic predictors of future weight gain [38]. These results emphasize the added usefulness of a metabolomics approach in identifying psychiatric patients at risk of developing metabolic comorbidities [38]. To begin to address the variability in treatment response commonly found in psychiatric disorders, serum metabolites were investigated in 8 schizophrenia patients before and after risperidone mono-therapy together with healthy controls. Although the sample size was small, partial least squares discriminant analysis model derived from GC-MS spectra revealed clear separations not only between schizophrenia and controls, but also between risperidone responders and non-responders [39]. These data suggest a global change of metabolites after risperidone treatment, and disturbances of energy metabolism, antioxidant defense systems, neurotransmitter metabolism, fatty acid biosynthesis, and phospholipid metabolism in schizophrenia, which could be partially normalized by risperidone therapy [39].

In major depressive disorder, at least 17 peripheral blood mononuclear cell -derived metabolites identified in the GC-MC platform were significantly altered when compared with controls, indicating disturbances of energy and neurotransmitter metabolism [40]. In a urinary metabolomics study, the NMR- and GC-MS– based methods identified two sets of metabolites that effectively discriminate “moderate” and “severe” patients from healthy controls, respectively [41]. These metabolites implicate involvement of gut microbial metabolites, glycine biosynthesis, and cell death and survival in MDD [41].

Depression is heterogeneous in its presentation and pathophysiology, affecting people of all ages, including those with medical diseases. Metabolomic analysis of plasma from older adults with and without depression revealed lower levels of several neurotransmitters and medium chain fatty acids in depression. Also, the profile of those with remission from depression was more similar to non-depressed controls than to the depressed individuals [42]. In a medical cohort of patients with heart failure with and without depression, GC-MS and LC-MS platforms revealed higher concentrations of several amino acids and dicarboxylic fatty acids [43], consistent with prior findings in neurotransmitter systems and fatty acid metabolism dysregulation. These results suggest that metabolomics biomarkers might be useful as objective diagnostic tests for depressive disorder. Based on findings in several untargeted metabolomics studies of depression and pharmacometabolomic studies [44, 45], a new study investigating whether these metabolites (sphingomyelins, lysophosphatidylcholines, phosphatidylcholines, and acylcarnitines) could act as predictors of depression recovery found that the addition of metabolites in all predictive models outperformed models without these metabolites [46].

In bipolar disorder, 1H-NMR-based analysis revealed lipids, lipid metabolism-related molecules, and some amino acids that distinguished bipolar subjects, with 7 specific markers as “key metabolites” [47]. A study using dual platform (NMR spectroscopy and GC-MS) revealed 5 urinary metabolite biomarkers with higher accuracy than single-platform derived markers in discriminating bipolar disorder from healthy controls [48]. In another study, an increased proportion of serum sphingolipids and glycerolipids and a decreased proportion of

glycerophospholipids were found in bipolar disorder patients when UltraPerformance LC coupled with high-resolution MS was used [49]. However, of the top 5 most differential lipids identified, 3 had unknown biology and could not be identified in any databases [49].

10.6 Polyunsaturated Fatty Acids in Psychiatric Disorders

While advances in mass spectrometry have expanded our knowledge of the patterns of metabolomic perturbation in psychiatric disorders, non-genetic risk factors such as diet play a major role in neuronal fitness [50–52]. Essential fatty acids represent a modifiable risk factor for neuropatho-physiological processes [53, 54]. While a number of hypotheses exist for etiology of psychiatric disorders, inflammation has recently been shown to play a role in common mental disorders such as depression [55] and schizophrenia [56].

Bioactive lipid mediators are a class of under-appreciated, under-utilized molecules in studies of inflammation. Specifically, the bioactive metabolites derived from fatty acids, termed eicosanoids, participate in modulation of inflammation [57, 58] and pain [59], and have been shown to affect risks of hypertension [60], cardiovascular diseases [61], cancer [62], anorexia nervosa [63], and schizophrenia [64]. To more comprehensively assess how dietary-based intervention [65] may affect inflammation and psychiatric outcomes [66–68], MS technology has been extended to lipidomics analysis for polyunsaturated fatty acids (PUFA) [69, 70]. These lipids include the 18-carbon “essential” PUFA such as linoleic acid (LA; 18:2n-6) and alpha-linolenic acid (ALA; 18:3n-3), 20-carbon PUFA arachidonic acid (ARA; 20:4n-6) and eicosapentaenoic acid (EPA; 20:5n-3), and 22-carbon PUFA such as docosapentaenoic acid (DPA; 22:5) and docosahexaenoic acid (DHA; 22:6n-3).

The clinical benefits observed when supplementing n-3 PUFA in inflammation-driven diseases were the initial clues that n-3 PUFA may similarly yield symptom relief in psychiatric disorders.

Rheumatoid arthritis patients who took n-3 fatty acids supplementation showed significant clinical benefits compared with those who did not receive n-3 supplementation [71]. Patients with colon cancer who received fish oil supplementation had a significant reduction in IL-6 and TNF-alpha levels and an increase in the percentages of CD3+ and CD+ lymphocytes when compared with the control group [72]. These data suggest that n-3 PUFA might also benefit symptoms in psychiatric disorders [73], which are now recognized as disorders of neuronal inflammation [74–76].

Peripheral levels of PUFA and n-6:n-3 PUFA ratios have been investigated in depressive disorder and bipolar disorder, the two most common mood disorders. The erythrocyte membrane ARA and DHA were significantly reduced in Taiwanese patients with bipolar disorder patients when compared with healthy controls, while no differences in total PUFAs were observed [77]. Similarly, in a sample of Italian patients with bipolar disorder, plasma DHA was significantly lower than that of healthy controls; however, EPA, AA, ALA, and ARA appeared to be elevated. Based on this result, the authors suggest that DHA may be a useful adjuvant for bipolar disorder [78].

To account for the competitive biology between the n-3 and n-6 classes of PUFA, another group analyzed a broad panel of serum lipids including PUFA in individuals with euthymic bipolar, depressive bipolar, major depressive disorder, and non-psychiatric controls. They found that higher AA:EPA and AA:EPA + DHA ratios were consistently found in the group with bipolar depression. Moreover, the AA:EPA + DHA ratio was positively correlated with depression severity in all groups, despite a lack of control on the fasting status of the subjects [79]. In another study, a high n-6:n-3 ratio and low DHA were found to be predictive of suicide risk among depressed patients [80], highlighting the potential prognostic role PUFA markers may play in depression. Lastly, several eloquent meta-analyses have examined evidence of the efficacy of treating depression or depressive symptoms with n-3 PUFA. Some took a conservative position, stating that the antidepressant efficacy of n-3 PUFAs in unipolar and bipolar depression cannot be confirmed until further replication with more “homogeneous” and larger samples [81]. Two independent meta-analyses reported n-3 PUFA supplementation, especially EPA, to be effective in treating major depression disorder and depressive symptoms [54, 82].

Schizophrenia is a serious psychiatric disorder that has been proposed as “neurodevelopmental” based on early subclinical brain imaging characteristics [83]. Decreased levels of AA and DHA were observed in never-medicated first-episode schizophrenia patients compared with medicated patients and healthy controls [84]. In another study using established schizophrenia cases and carefully selected matched controls, DHA, DPA, and DHA:ARA ratio were reduced in patients compared to controls [85].

For another psychiatric disorder, anorexia nervosa, we found the ARA:EPA ratio to be *lowered* in anorexia nervosa compared with healthy controls [63]. To determine if PUFA levels were “risk factors” or “consequences” of schizophrenia, ultra-high risk individuals (for developing schizophrenia) were followed and dietary intake was assessed. Those who later developed psychosis were found to consume more dietary n-6 PUFAs (LA, AA) and had higher AA:EPA + DHA ratios than those who did not develop psychosis [86]. Similarly, n-3 PUFA supplementation was associated with beneficial effects for anorexia nervosa in several studies [87, 88]. Together, these data support a possible protective role n-3 PUFAs play in preventing onset or worsening of psychotic symptoms. Several mechanisms have been proposed to explain n-3 PUFAs’ favorable effect in psychiatric disorders, including anti-neuronal inflammation [89] and neuronal protection [90].

Although the data in psychiatric literature largely paint a favorable view for supplementation of n-3 PUFA, the verdict on the supplements’ therapeutic role in psychiatric disorders cannot be established without randomized clinical trials with well-characterized longitudinal data and large sample size. While many independent studies in the past have supported the benefits of n-3 PUFAs for serious medical disorders such as cardiovascular disease and cancer, the most recent meta-analysis showed that n-3 fatty acids did not reduce the incidence of cancer and cardiovascular events (e.g., stroke, myocardial infarction, and cardiovascular event-related death) [91]. In a large randomized trial including 15,480 diabetic patients without cardiovascular disease, no significant difference was found in the risk of serious vascular events between those who were assigned to n-3 PUFA supplementation and those who were assigned to a placebo [92]. It is thus imperative to

conduct further research not only to confirm the effectiveness of n-3 PUFAs in psychiatric disorders but also to explore molecular mechanisms driving clinical benefits in patients and develop biomarkers to classify individuals with high likelihood of benefiting from PUFA supplementation. To achieve these goals, the logical next step is to take advantage of targeted metabolomics technology to focus on a specific class of metabolites, termed eicosanoids [93, 94].

10.7 Eicosanoids as Biomarkers for Psychiatric Disorders

While the pattern of association between PUFA and psychiatric disorders may at first seem straightforward, one must understand the functions and mechanisms underlying beneficial effects of any compound to use such benefits clinically. The bioactive lipids family represents the next logical class of molecules to study to elucidate PUFA mechanisms, and to establish a biomarker system that is biologically and clinically informative to guide precision psychiatry.

Major n-6 and n-3 PUFA can be oxygenated by at least 3 different enzymes to synthesize over 120 heterogeneous and pleiotropic bioactive molecules termed eicosanoids [59, 95]. While the word eicosanoid was derived from the Greek word “eikosa,” meaning “20,” based on the derivatives of the 20-carbon ARA, here “eicosanoid” is applied to also include the oxygenated products of other PUFA including LA, ALA, DHA, and DPA. The 3 enzymatic families that affect PUFA are cyclooxygenases 1 and 2 (COX-1/2); 5-, 12-, and 15-lypooxygenases (5/12/15-LOX); and P450 epoxygenase. The COX-1/2 are known to drive the synthesis of prostanoids such as prostaglandins and thromboxanes, while 5/12/15-LOX produce leukotrienes, lipoxins, and hydroxyeicosatetraenoids, and P450 synthesize HETEs and epoxyeicosatrienoids [95]. The eicosanoids most well-studied for their link to inflammation biology include prostaglandin E2 (PGE_2), a pro-inflammatory molecule stimulated by COX, and 5-LOX-produced leukotrienes, which contribute to potent inflammation in asthma and other allergic diseases [96]. CYP regulates inflammation by oxidizing ARA with its active heme iron to form anti-inflammatory HETE or epoxy-eicosatrienoic acid (EETs), which is then hydrolyzed into pro-inflammatory dihydroxyeicosatrienoic acids (DHET) by soluble epoxide hydrolase (sEH) [97].

We have demonstrated the effectiveness of a combined use of lipidomics and targeted metabolomics in investigating anorexia nervosa, an illness characterized by rapid weight loss and reduction in food consumption [63]. Higher ratios of dihydroxy to epoxy fatty acids were found in anorexia nervosa patients than in controls, suggesting an upregulation of sEH activity, an elevation in pro-inflammatory eicosanoid profile, and a reduction in anti-inflammatory epoxy fatty acids [63]. Additionally, recovered anorexia nervosa patients showed a partial normalization in PUFA and eicosanoids, implying the resolution of inflammation and that it may be achieved by dietary intervention [26]. This is clinically relevant as well for patients with other types of psychiatric disorders because medication non-adherence rate is notoriously high, up to 80% in schizophrenia [98]. Dietary intervention may be an important alternative treatment modality for patients refusing medications.

The results of the anorexia nervosa study suggest that psychopathology and inflammatory processes in eating disorders are affected by interactions between dietary PUFA and genetically driven metabolism. With additional empirical research, food-based treatment or a nutraceutical strategy may be employed to improve outcomes in clinical psychiatry. Furthermore, as eicosanoid variation reflects *in vivo* cellular inflammation, targeted metabolomics can be applied to develop improved prognosis biomarkers.

Untargeted metabolomics emerged as a useful tool to uncover unsuspected pathways involved in psychiatric disorders, and a targeted metabolomics approach is particularly helpful in characterizing the specificity, direction and magnitude of disease-associated metabolites, which provide molecular insight helpful to develop new treatments. In a pilot study of adolescent major depressive disorder, we characterized eicosanoids in fasting plasma at the baseline visit and final visit after a 2 year follow-up period. While all subjects displayed no difference in depression severity or profile of depression risk factors at the baseline visit, half of the subjects had progressed to significantly worse depression (refractory group) while the other half remitted. Strikingly, the eicosanoids profile in the refractory group revealed a pattern very similar to that found in patients with anorexia nervosa [99], implicating an epoxy fatty acid catalyzing enzyme, soluble epoxide hydrolase (sEH), as a common risk factor for depression and anorexia nervosa.In a study of seasonal major depression [31], quantitative changes of CYP450 pathway eicosanoids during the winter season (when subjects experienced severe depression symptoms) were similar in pattern to the eicosanoids profile we found in the refractory adolescent depression group [99], suggesting that sEH-mediated metabolism of PUFA eicosanoids underlies the psychopathology of depressive disorders [31].

sEH is known as a regulator of inflammatory resolution due to its potent and complex mechanisms in the formation/catabolism of epoxy- and diol eicosanoids [100], but its involvement with psychiatric phenotypes was only recently uncovered through MS-based discovery [31, 99] and sequencing [101]. Another group has since demonstrated that sEH inhibition showed antidepressant effects in both inflammation and social defeat stress models of depression [102] and attenuated behavioral abnormalities (i.e., hyperlocomotion and prepulse inhibition deficits) in an animal model of schizophrenia [103]. Moreover, a higher level of sEH was found in postmortem brain samples from patients with depression, schizophrenia, and bipolar disorder compared with control samples [102], strengthening the role sEH plays in psychiatric pathology.

The discovery of an association between cytochrome P450-associated bioactive lipid mediators and psychiatric disorders is made possible in part because of advances in technology, but the involvement of eicosanoids in psychiatric disorders was reported as early as the 1980s. Using low throughput techniques such as radioimmunoassay, elevated levels of PGE and PGE2 were identified in schizophrenia [104, 105], whereas PGD2, PGE2, and PGF2α and TXB2 were found to be elevated in major depressive disorder [106–109]. Almost 40 years later, the field can now take advantage of both untargeted and targeted liquid chromatography-mass spectrometry-based methods to monitor a much larger number of potential markers. A recent schizophrenia study that investigated 158 markers including PUFA, eicosanoids, and related mediators from enzyme-dependent or independent pathways

uncovered 23 metabolites that were significantly altered in patients compared with healthy controls [64]. While some abnormal markers were reversed after antipsychotic treatment, anandamide, oleoylethanolamine, and ARA were identified as having the best potential for differentiating patients from controls [64].

Leveraging what is already known about the biology of bioactive lipids and the plethora of physiological and homeostatic processes they participate in, several drugs have already been developed to inhibit the production of pro-inflammatory mediators, including nonsteroidal anti-inflammatory drugs (NSAIDS) that reduce the activity of both COX-1 and COX-2 [110], cysteinyl leukotriene (cysLT) receptor antagonists that reduce bronchoconstriction caused by cycLT and pro-inflammatory cytokines in the pulmonary system [111], and COX-2 inhibitors [112]. In fact, administration of COX-2 inhibitor celecoxib has been shown to improve symptoms in schizophrenia [113], possibly through inhibiting conversion of ARA into prostanoids. Additionally, COX-2 inhibitors may be effective as an adjunctive treatment by accelerating the onset of antidepressant effects for bipolar depression and refractory major depression [114, 115].

10.8 Conclusions

While an untargeted metabolomics strategy has gained popularity for its ability to screen new and unsuspected pathways involved in psychiatric disorders, evidence of a role for eicosanoids in psychiatry is accumulating. Eicosanoids participate in the modulation of inflammatory processes and affect the risk of a number of neuropsychiatric disorders. Characterizing the eicosanoid signature in major psychiatric disorders and subtypes within can lay the foundation for individualized treatment approaches. Much work is needed to develop psychiatric multi-omics biomarkers that would not only predict risk, but could also offer an individual-specific course of disorder and responses to therapeutics. For example, studies identifying metabolomic changes during the course of psychiatric disorders are lacking. Additionally, almost all studies used bio-specimens taken from blood or urine and not from the organ of disease origin, the brain. This limits researchers' ability to identify brain region-specific metabolite changes and mechanisms in human samples. Follow-up studies using model animals are critical to further research metabolome read-out and neuronal mechanisms to better define pathophysiology of psychiatric disorders. That being said, when coupled with other omics strategies, metabolomics provides a platform for clarifying the relationship among host factors (e.g., genetic variation), substrates (e.g., dietary profile), and downstream metabolomic perturbation and implicated biology. The end knowledge will improve the clinical utility of a multi-omics biomarker system on diagnostic, prognostic, and therapeutic fronts.

While emerging data already indicate beneficial effects of pharmacological agents such as COX-2 and sEH inhibitors, another unique characteristic of eicosanoids is that their substrate availability required for synthesis can be altered by dietary intake or supplementation of PUFA. This opens the door for development of a nutraceutical approach in psychiatric therapeutics. Although there are still many challenges to be addressed and further studies are required to elucidate the complex role of eicosanoids in the psychopathology of psychiatric disorders, metabolomics coupled with other multi-omics

approaches can (1) provide deeper insights into the biological underpinnings of psychiatric disorders, (2) be used as powerful diagnostic, disease-monitoring, and treatment response biomarkers, and (3) bring precision psychiatry closer to reality by enabling improved drug discovery and development processes, thereby advancing pharmacometabolomics, nutrigenomics, and metabolomic engineering technologies.

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