Psychotic Bipolar Disorder

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Abstract

Psychotic symptoms are considered a clinical predictor of poor outcome in bipolar disorder (BD). The misdiagnosis of psychotic BD (BD-P) with schizophrenia, schizoaffective disorder, or delusional disorder is very common. The identification of biological markers for BD-P would contribute to establish an early diagnosis and to define a proper treatment, to improve outcome of BD-P patients.

A case of a patient suffering from BD-P has been described, focusing on neuroimaging, neuropsychological, and inflammation data that could be considered potential biomarkers of BD-P.

The patient was a 36-year-old female. During her two hospitalizations, inflammatory and metabolic markers were all normal, except for lower plasma levels of vitamin A. After giving her written informed consent, epigenetic tests were performed, showing a significantly different expression of some miRNAs than healthy controls (HC). The magnetic resonance imaging (MRI) showed hypoplasia of the cerebellar vermis and a small left peritrigonal area of hyperintensity in T2 sequence. The only neuropsychological deficit appeared in the motor task. The positron emission tomography (PET) showed a bilateral hypermetabolism in the frontal cortex, cingulate, and striatum.

This case demonstrated that biological markers may be useful to predict outcome of psychotic bipolar patients.

Keywords

Bipolar disorder · Psychotic symptoms · Biomarkers

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4.1 Introduction

Bipolar disorder (BD) is a clinical condition that affects about 1–2% of the adult population. It is associated with a high disability and risk of chronicity, particularly if not promptly treated [1]. The identification of potential specific and objective biomarkers could provide an important support to better understand the course of illness, the mechanisms of vulnerability and of disorder expression, finally contributing to the clinical decision-making process.

For example, a recent study has demonstrated the presence of an increased level of a combined inflammation score (IgG class antibodies to the NR2 peptide fragment of the *N*-Methyl-D-Aspartate (NMDA) receptor, IgG class antibodies to gliadin, IgG class antibodies to the Mason-Pfizer monkey virus gag protein, IgM class antibodies to Toxoplasma gondii) in a sample of 57 manic patients, compared to healthy controls (HC) [2]. Moreover, a review analyzed the role of inflammatory cascade and brain-derived neurotrophic factor (BDNF) in cardiovascular diseases among bipolar patients, remarking the importance of BDNF and inflammatory cascade as possible markers of BD [3]. The reason for the elevation of inflammatory markers in individuals with mania remains unknown, but these findings suggest the presence of specific markers in bipolar patients that are not identifiable in the control group. Furthermore, a recent paper describing the work of the Biomarkers Network from the International Society for Bipolar Disorders (ISBD-BIONET) cited neuroimaging and genetic findings in bipolar disorder as important tools to identify bipolar patients (e.g., the loss of gray matter, the altered activation of anterior temporal, the ventral prefrontal and subcortical regions in response to emotional stimuli, the identification of several potential candidate genes associated with increased risk for developing BD) [4]. A review by Schroeter et al. [5] reported that increased serum levels of S100B, a glial growth and differentiation factor, are more frequently present in patients with mood disorders than in HC, particularly in major depressives.

Bipolar patients may experience delusions/hallucinations both during depressive (up to 45% of cases) [6, 7] and manic episodes (up to 88% of cases) [8], and it has been demonstrated that psychotic bipolar patients (BD-P) had better prognosis than schizophrenia (SKZ) patients [9] but worse than non-psychotic bipolar disorder (BD-NP)/unipolar patients [10, 11] in terms of more severity of illness, greater morbidity [12], longer hospitalizations [13], and more frequent relapses [14]. In particular, BD-P patients experiencing mood-incongruent delusions were found to present shorter euthymia and more frequent hearing hallucinations than BD-P patients with mood-congruent delusions [15]. If psychotic symptoms occurred during a depressive episode, the risk of relapse was greater for BD-P with respect to BD-NP [16] than in the case of psychotic mania [12], and the presence of psychotic symptoms in patients with a major depressive episode (MDE) was predictive of non-remission after a standard psychopharmacological treatment [17].

The diagnosis of psychotic BD is not always prompt, and, as a consequence of misdiagnosis (up to 61%) with SKZ, schizoaffective disorder, and delusional disorder, an appropriate treatment of psychotic bipolar patients may be delayed with consequently increased suicidal risk, increased social impairment and higher social costs [18, 19]. Although biological markers for the subset of BD-P have been little

investigated, it becomes increasingly clear that the identification of biomarkers for BD-P is important. First, in the light of the high rate of misdiagnosis, biological markers of psychotic BD would help clinicians to establish an early diagnosis; moreover, as longer duration of untreated illness (DUI) in psychotic BD has been related to lower Global Assessment of Functioning (GAF) scores and more hospitalizations [20], biomarker identification would provide the possibility of clinical staging and would help to ameliorate outcome in the long term by recognizing the disorder early and defining a prompt and personalized treatment [21].

4.2 Case Presentation

E. was a 36-year-old woman, graduated in economics, twice hospitalized in our inpatient clinic. She has been described by her relatives as a diligent and scholarly girl, with few friends and the preference for solitary hobbies. Good school performance is reported up to the first year of university, when the patient started to reduce the number of approved exams during each session, however keeping a good overall performance and earning a 3-year degree in 6 years.

Family members reported a depressive episode that occurred during the college period, following the death of the mother in 2008. It was characterized by anhedonia, depressive mood, abandonment of work, and suicidal ideation without concrete projects. The patient turned to a psychotherapist, initially at the Community Mental Health Center affiliated to our Psychiatry Department, and then to a private psychoanalyst with whom she is still in care.

After graduation, the patient undertook apprenticeship at an accountant's for a year and a half. This period is described by relatives as very stressful for the high demands of work. The patient resigned and started working with her father who is also an accountant, but the office was closed down in March 2016 for discontinued activity, and, since then, the patient has been unemployed.

Until this moment, the patient has never taken psychopharmacological therapy, with the exception of a symptomatic treatment (benzodiazepines) prescribed by the general practitioner.

In November 2016 the patient reached our emergency department after a few days of excitement, subtotal insomnia, loosening of associative links, logorrhea, persecutory delusions, and psychomotor agitation symptoms. She was poorly accessible to conversation, agitated, with oscillating mood. Electrocardiogram was performed, and clonazepam 15 drops + promazine 15 drops were administered. She was unaware of the need for care; nevertheless she voluntarily accepted hospitalization, and then she was admitted to our inpatient clinic.

On admission, E. showed euphoric mood, purposeless excessive motor activation, megalomaniac and persecutory delusions, unstable sensitivity, and insomnia. The physical examination and routine blood tests were normal, and the urine drug test was positive for opioids.

At baseline, the Brief Psychiatric Rating Scale (BPRS) [22] was administered with a total score of 43. Young Mania Rating Scale (YMRS) [23] was 27, and Hamilton Scale for Depression (HAM-D) [24] was 17. Her first pharmacological

treatment included lithium up to 600 mg/day, haloperidol up to 2 mg/day, and intramuscular olanzapine up to 20 mg/day.

After giving her written informed consent, specific blood tests were carried out, measuring inflammatory markers (total lymphocyte count, B lymphocyte count, T lymphocyte count, C-reactive protein, serum albumin, serum bilirubin, serum uric acid, vitamins A and E) and performing a genetic test (miRNA-wide analyses), showing a significantly different expression of some miRNAs than HC. Of note, E. presented an overexpression of hsa-miR-579-3p, hsa-miR-4454 + hsa-miR-7975, and hsa-let-7a-5p. All inflammatory markers were normal, except for vitamin A which was 0.27 mg/L (normal range 0.30–0.70 mg/L).

During hospitalization, she underwent a magnetic resonance imaging (MRI) showing a mild hypoplasia of the cerebellar vermis (Fig. 4.1).

Furthermore, the patient underwent neuropsychological examination showing normal scores in language, verbal memory, working memory, frontal efficiency test, and a deficit in motor functioning (Table 4.1).

After 1 week of hospitalization, the BPRS score decreased to 27, MRS was 11, and HAM-D was 9. The patient was collaborating and calm, and mood improvement was observed. Speaking was fluid, and associative links were more frequently maintained. Delusions gradually disappeared, and the patient became aware of the need to continue treatment and visits. She was discharged with olanzapine 20 mg/day and lithium 900 mg/day, and the indication for follow-up at our Day Hospital Unit and at the Community Mental Health Center affiliated with our department.

Box 4.1 First Hospitalization

- Admitted with a possible manic episode with psychotic symptoms
- Urine drug test positive for opioids
- Vitamin A (antioxidant) lower than normal range
- miRNA
- MRI: mild hypoplasia cerebellar vermis
- BPRS 43 → 27; HAM-D 17 → 9; MRS 17 → 11
- Discharged with olanzapine 20 mg/day + lithium 900 mg/day

She attended our Day Hospital on three occasions, where the psychiatrist did not change the treatment with olanzapine and lithium. She was cooperative and appropriate to the context. Initially abundantly logorrheic and easily distracted, her speech gradually returned to normality, and associative links were maintained. The sleep rhythm was preserved.

In December 2016 she attended the Community Mental Health Center affiliated with our department. Olanzapine was suspended for hypersomnia, and a depressive nuance appeared, without evolving into an MDE. Lamotrigine was prescribed in order to stabilize the subthreshold depressive symptoms. In May 2017 the patient attended the last psychiatric visit at the Community Mental Health Center, and she was treated with lithium 600 mg/day and lamotrigine 200 mg/day.

E. maintained a good psychopathological compensation until the end of May, when she was accompanied to the emergency department by public forces for

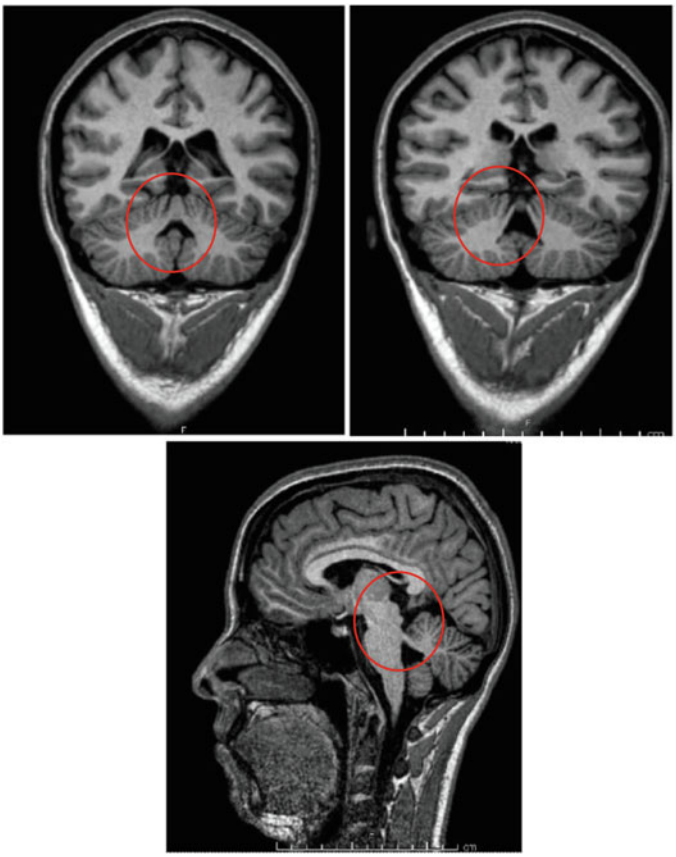

Fig. 4.1 T1-weighted sagittal and coronal images showing mild hypoplasia of the cerebellar vermis

Table 4.1 Neurocognitive evaluation (BACS subtest and Beck Cognitive Insight Scale)

Test	Normal range	Score	Equivalent score	Comment
Language				
Verbal fluency (*subtest BACS*)	v.n. $\geq$ 31.68	45.25	2	Normal
Memory				
Verbal memory (*subtest BACS*)	v.n. $\geq$ 33.01	50.00	4	Normal
Motor function				
Token task (*subtest BACS*)	v.n. $\geq$ 68.77	67.00	0	***Deficit***
Symbol-coding task (*subtest BACS*)	v.n. $\geq$ 40.49	58.75	4	Normal
Frontal efficiency tests				
Working memory (*subtest BACS*)	v.n. $\geq$ 14.93	23.25	4	Normal
Tower of London test (*subtest BACS*)	v.n. $\geq$ 12.37	22.00	4	Normal

	Score	Comment
Beck cognitive insight scale	8	The patient has insight

behavioral abnormalities in a library. Symptoms such as insomnia, excessive expenses, accelerated thinking with loose associative links, and megalomaniac delusions were reported. She was hospitalized for 2 days in another hospital and treated with lithium up to 900 mg/day, levomepromazine up to 50 mg/day, and olanzapine up to 20 mg/day. She was fatuous and hilarious, overall manageable; the ideation was abundant with loose links and delusions without emotional participation. Hallucinations were not detectable. She showed attention and concentration deficit. The hypnotic profile was restored and, after two days, she was moved to our inpatients clinic.

During hospitalization, treatment with lithium 900 mg/day and intramuscular aripiprazole up to 30 mg/day was prescribed in anticipation of long-acting treatment.

Lithium plasma levels were 0.91 mEq/L with lithium 900 mg/day. Augmentation therapy with folic acid was prescribed because routine blood tests showed mild normocytic anemia with folate deficiency.

E. showed a gradual return to euthymia. Associative links were more frequently maintained and megalomaniac delusions resolved. After 1 week of hospitalization, E. underwent long-acting intramuscular therapy with aripiprazole 400 mg which was well tolerated by the patient. Furthermore, as diagnostic completion, E. underwent another MRI which showed a small left peritrigonal area of hyperintensity in T2 sequence (Fig. 4.2) and a positron emission tomography (PET) showing bilateral hypermetabolism in the frontal cortex, cingulate, and striatum (Fig. 4.3).

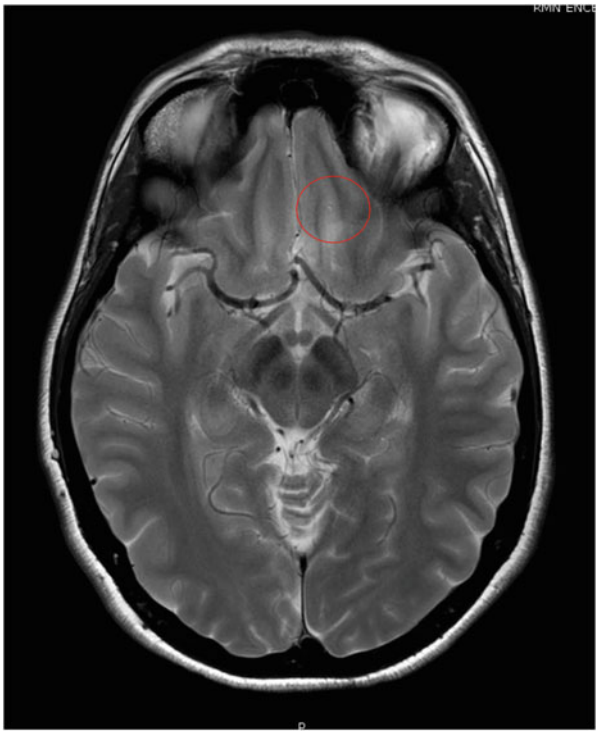

Fig. 4.2 T2-weighted image showing a mild left peritrigonal hyperintensity

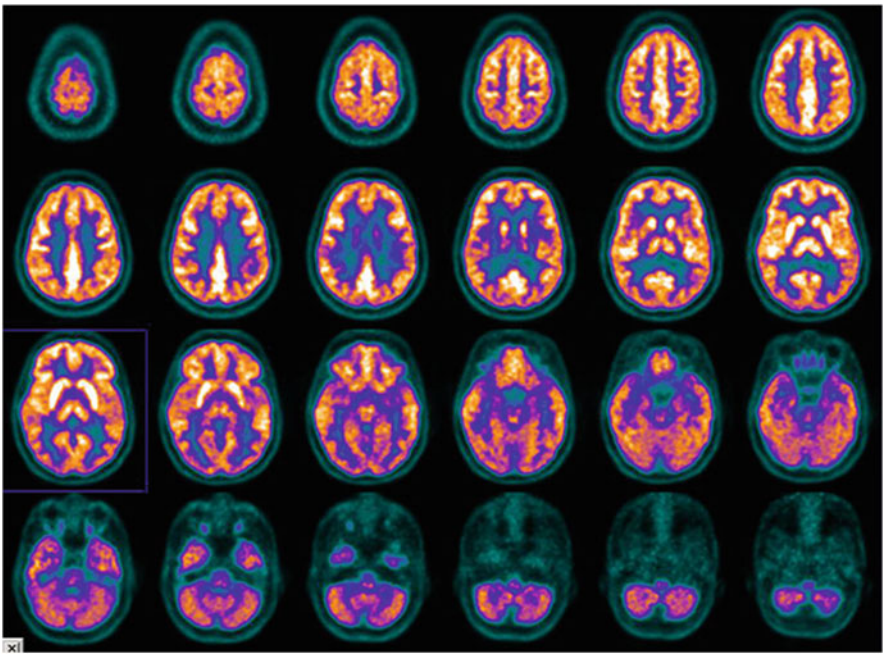

Fig. 4.3 FDG-PET shows bilateral hypermetabolism in the frontal cortex, cingulate, and striatum

After 1 week of hospitalization, the patient was discharged with lithium 900 mg/day, aripiprazole 15 mg/day, folic acid 5 mg/day, and indication to be followed-up at our Day Hospital Unit for the long-acting treatment.

Box 4.2 Second Hospitalization

- Admitted with a possible manic episode with psychotic features
- Treated with lithium 900 mg/day and aripiprazole 30 mg/day
- Lithium plasma levels = 0.91 mEq/L
- MRI: small left peritrigonal hyperintensity
- PET: bilateral hypermetabolism in the frontal cortex, cingulate, and striatum
- Discharged with depot treatment with Aripiprazole Maintena 400 mg + aripiprazole 15 mg/day + lithium 900 mg/day

Lithium plasma levels were 0.9 mEq/L while taking lithium 900 mg/day. At the Day Hospital, she showed a good psychopathological compensation, although she complained about asthenia. Aripiprazole was suspended, and she continued the stabilizing treatment with lithium 600 mg/day and weekly controls. After 1 month, lithium plasma levels decreased to 0.39 mEq/L, and the treatment was increased to lithium 750 mg/day.

Currently, depot treatment with Aripiprazole Maintena 300 mg is administered monthly, and she is taking lithium 750 mg/day, presenting a good compensation and a good psychosocial functioning.

4.3 Review of the Literature

Biological markers of psychotic bipolar disorder have been little investigated. A recent systematic review showed that most of the studies in literature are concordant in recognizing BD-P as a subset with specific biological abnormalities, with a different degree of severity with respect to SKZ and BD-NP [25].

From a genetic point of view, the most studied genes are NRG1, 5HTTLPR(s), COMT, and DAOA, with inconclusive results. The finding concerning the positive association between mood-incongruent BD-P and one NRG1 polymorphism (NRG241930G) has been replicated [26, 27], as well as the association between the psychotic dimension in BD and two chromosome regions (13q32 and 16p12) [28–30].

Studies of infectious, neuroendocrine, and inflammatory markers demonstrated that BD-P patients had higher levels of kynurenic acid (KYNA) [31] and lower serum levels of dehydroepiandrosterone sulfate (DHEAS) and progesterone than BD-NP [32] and increased anti-*Saccharomyces cerevisiae* antibodies (ASCA) levels than HC [33, 34], but these data have not been replicated yet.

Neurophysiological studies showed SKZ patients and BD-P patients sharing abnormal low-frequency activity [35]. Four papers reported reduced P50 suppression in BD-P compared to BD-NP/HC [36–39], while two studies did not find any differences [40, 41]. BD-P had higher M20 wave lateralization than BD-NP [42], higher P85 ratio [43] and an increased beta-gamma activity after P200 response window compared to HC [44], but these data need further studies to be confirmed.

Most of the functional neuroimaging studies have not been replicated. Data from structural neuroimaging showed that SKZ patients had lower gray matter volumes than BD-P [45–47]. Sensitive differences were found between BD-P and BD-NP, with contrasting results: the absence of major reduction of gray matter volumes has been replicated [48–50], as well as the lower DLPFC volume [51, 52] and the ventricular enlargement [53, 54]. These preliminary findings have to be replicated in further studies.

Finally, in neuropsychological studies, SKZ and BD-P resulted impaired in emotion processing and ToM compared to HC [55–57]. Lower scores of BD-P than BD-NP have been found in some cognitive domains (executive functioning, verbal and logical memory, working memory, verbal, and semantic fluency) by different authors [58–61]. However, three papers reported no differences between BD-P and BD-NP in terms of cognitive performance [62–64].

In the presented case, E. underwent genetic and neuroimaging examination and dosages of the inflammatory pattern. Her MRI showed a small left peritrigonal hyperintensity, which is in line with the previous findings that reported significantly more white matter hyperintensities in BD-P than in HC. The inflammatory markers

were all normal, except for vitamin A (retinol), which was lower than the normal values. The inflammatory pattern may vary according to the different phases of the disorder. Of note, it has been demonstrated that vitamin A deficiency contributed to the oxidative damage in developing rat brain [65] and that a supplementation therapy with nonenzymatic antioxidants (such as vitamin A) significantly reduced anxiety and depression in a psychiatric population [66]. Moreover, Chowdhury et al. [67] found significantly lower concentrations of antioxidants (vitamins A, E, and C) in BD patients than in HC.

From a clinical point of view, the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) demonstrated several overlaps between SKZ and BD-P in terms of symptomatology, psychosocial functioning, and family characteristics [68]; furthermore, the presence of overlapping biological abnormalities with SKZ, but with a lesser degree of severity, suggested that BD-P is an intermediate phenotype between psychotic and mood disorders and part of the "psychotic continuum" [69]. Of note, a growing body of data in literature indicates that different biological markers are associated with the psychotic dimension in BD, but further research is needed to detect specific biomarkers of BD-P. Taken together, these findings are in favor of the hypothesis of the presence of a continuum among psychotic disorders, suggesting that a dimensional model may be more reliable than a categorical one.

Box 4.3 Biomarkers of BD-P

- *Genetics*: NRG1 polymorphism (NRG241930G) and two chromosome regions (13q32 and 16p12)
- *Neuro-immuno-endocrinology*: ↑KYNA, ↑ASCA, ↓ DEAHS and progesterone
- *Neurophysiology*: ↓ P50 suppression, ↑ P85 ratio vs HC, ↑ β-γ activity after P200 response window, ↑ M20 wave lateralization
- *MRI*: ↓ DLPFC volume (mood incongruent), ↓ DLPFC and insula volumes, ↓ left vlPFC, dmPFC, left temporal pole volumes, ↑ **white matter hyperintensity**
- *Neuropsychology*:↓ executive functions, ↓ verbal and logical memory, ↓ (spatial) working memory, ↓ verbal and semantic fluency, ↓ verbal learning, ↓ visual attention, ↓ emotional processing

Key Points

- BD is a chronic disorder associated with high disability and morbidity. Some biological abnormalities have been reported in BD as an attractive basis for the discovery of promising biomarkers, such as the loss of gray matter, the altered activation of anterior temporal, ventral prefrontal and subcortical regions in response to emotional stimuli, and increased level of a combined inflammation score during mania.

- Psychotic bipolar disorder seems to be a specific subset, characterized by oscillating mood and the presence of psychotic features. Patients suffering from BD-P have worse prognosis than BD-NP in terms of more severity of illness, greater morbidity, longer hospitalizations, and more frequent relapses.
- The rate of misdiagnosis of BD-P is high, up to 61%. BD-P is more often misdiagnosed with schizophrenia, schizoaffective disorder, and delusional disorder, thus delaying the prescription of an appropriate treatment, with consequently increased suicidal risk, increased social impairment, and higher social costs.
- Several findings in the field of mood disorders could provide the background for the identification of potential specific and objective biomarkers, which could be an important aid to better understand the course of illness, the mechanisms of vulnerability and of disease expression. Biological markers of psychotic BPAD would help clinicians to establish an early diagnosis and to ameliorate prognostic evaluations.
- To date, only few studies about potential biological markers of BD-P have been replicated. Among these are the association between BD-P and NRG1, 5HTTLPR(s), COMT, and DAOA genes; data about BD-P and 16p12/13q regions; increased IL-1 and IL-6 plasma levels in both BD-P and SKZ; higher lateralization of M20 wave and higher P85 ratio in BD-P than HC; reduced white matter integrity than HC; and more severe cognitive impairment than BD in the same domains and an intermediate cognitive performance between SKZ and HC.

Self-Assessment

1. What is the prevalence of bipolar disorder?
   (a) 5%
   (b) 20%
   (c) 80%
   (d) 1–2%
   (e) 10%
2. Which abnormality has been found in manic BD patients?
   (a) Increased BDNF levels
   (b) Increased inflammatory markers
   (c) Decreased inflammatory markers
   (d) Increased serum antioxidants levels
   (e) Decreased BDNF levels
3. Psychotic bipolar patients present:
   (a) Worse prognosis than unipolar and BD-NP patients
   (b) Better prognosis than unipolar and BD-NP patients
   (c) Worse prognosis than SKZ patients
   (d) Better prognosis than schizoaffective patients
   (e) We do not have data about BD-P patients' prognosis
4. Identification of biological markers for BD-P:
   (a) Would hinder the diagnostic and therapeutic process

(b) Could help patients to decide independently which treatment is the best
(c) Would help clinicians to promptly diagnose the disorder and to properly identify the treatment
(d) Could help clinicians to decide independently which treatment is the best
(e) Would hinder the clinical staging processing, worsening outcome in the long term

5. Vitamin A (retinol) is:
(a) The forerunner of beta-carotene
(b) An enzymatic antioxidant
(c) Fundamental for metabolism of lipids and proteins
(d) A cholesterol derivative
(e) A nonenzymatic antioxidant

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