Journal of Affective Disorders 294 (2021) 159–162

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Short communication

Gamma oscillations predict treatment response to aripiprazole in bipolar disorder

Mehmet Kemal Arıkan [a,*], Güven Günver [b], Reyhan İlhan [a], Özden Öksüz [c], Baris Metin [d]

[a] Kemal Arıkan Psychiatry Clinic, Istanbul, Turkey
[b] Istanbul University, Department of Biostatistics, Istanbul, Turkey
[c] Yeditepe University, Department of Neuroscience, Istanbul, Turkey
[d] Uskudar University, NPIstanbul Brain Hospital, Department of Neurology, Istanbul, Turkey

ARTICLE INFO

Keywords:
Aripiprazole
Bipolar disorder
Gamma oscillations
qEEG
Resistance

ABSTRACT

Objective: Treatment of Bipolar Disorder (BD) is a challenging issue. Aripiprazole monotherapy is a recommended option for the treatment of mania in BD. The electrophysiological markers of treatment response to aripiprazole could be potentially identified by quantitative Electroencephalography (qEEG).
Methods: Twenty-four patients with BD were analysed retrospectively. Based on the percentage reduction in Young Mania Rating Scale, they were classified as responders (N = 14) and non-responders (N = 10) to aripiprazole monotherapy. Their resting-state qEEG recordings were examined. Spectral power across all frequency bands were calculated. Absolute powers for all frequency bands were compared between these groups.
Results: Independent sample Mann-Whitney U test revealed that patients who did not respond to aripiprazole had greater gamma power than aripiprazole treatment responders.
Conclusions: Based on the present findings, it can be proposed that excess in gamma power could be the electrophysiological biomarkers of unresponsiveness to aripiprazole treatment in BD.

1. Introduction

Bipolar disorder (BD) is a common psychiatric disorder with a prevalence of about 2.4% (Rowland and Marwaha 2018). The disorder can affect a wide age spectrum and the peak incidence of onset is between 20 and 25 years (Pini et al. 2005). The etiology of bipolar disorder is complex and implicated factors range from genetic alterations to various psychological stressors including childhood traumatic experiences, infections and substance abuse (Rowland and Marwaha 2018).

Pharmacological decision for the treatment of BD should be made in a careful manner since it can be a challenge to ameliorate the symptoms of both mania and hypomania. From the ethical perspective, the right pharmacological decision is crucial for preventing non-suicidal self-injury and suicide which are related to traumatic childhood experiences, frequently reported in BD (Serafini et al., 2017a) and they are reflected to increased standardized mortality ratios (SMR) over the past two decades (Staudt Hansen et al., 2019). Current guidelines recommend the use of lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine alone or in combination for patients with mania (Yatham et al. 2018). On the other hand, there is limited data for guiding the clinician in determining the treatment agent. Although the guidelines encourage monotherapy, the success rates of monotherapy with antitypical antipsychotics may not be satisfactory and a combination of several medications is often necessary (Hui Poon et al. 2015). However, a combination approach would also create problems such as decreased treatment adherence and increased incidence of metabolic syndrome.

When optimal treatment agent cannot be reliably determined based on the clinical features, clinicians may benefit from incorporating biological measures that might predict treatment response. For BD, candidate biomarkers include hormones, neurotransmitters, genetic variations, neuroimaging parameters as well as electroencephalography (EEG) derived measures (Brand et al. 2015). Of those, EEG comes forward with being a low cost, noninvasive and reproducible examination.

Among EEG based biomarkers, fast gamma activity (30-50 Hz) is particularly important in that it reflects the efficacy of GABA transmission in the brain. Further, studies indicate that gamma activity plays a role in visual and emotional stimuli processing (D'Onofrio et al. 2015;

Abbreviations: AP, Absolute Power; BD, Bipolar Disorder; QEEG, Quantitative Electroencephalography.

* Corresponding author. Kemal Arıkan Psychiatry Clinic, Halaskargazi Street, No.103, Gün Apartments, Flat 4B, Osmanbey, Istanbul, 34371, Turkey.
E-mail address: mkarikan46@gmail.com (M.K. Arıkan).

https://doi.org/10.1016/j.jad.2021.07.044
Received 25 February 2021; Received in revised form 25 June 2021; Accepted 11 July 2021
Available online 16 July 2021

Fitzgibbon et al. 2004) and these functions are reported to be abnormal in BD patients (Serrafini et al., 2017b; Liu et al., 2014). According to the study of Kumar, Sinha, Tikka and Goval (2015), gamma activity is correlated to the number of previous episodes and treatment resistance in bipolar disorder. From this point on, we hypothesized that gamma activity can be used to predict treatment response to aripiprazole monotherapy in bipolar disorder.

2. Methods

The study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization/ Good Clinical Practice guidelines. All participants gave written informed consent, and the local ethics committee (Non-Interventional Research Ethics Board of Uskudar University) approved the study.

2.1. Participants

The study included 24 BD patients with manic episode identified retrospectively from Kemal Arikan Psychiatry clinic database based on the following criteria:

1 Medication free for ≥3 weeks.
2 A Young Mania Rating Scale (YMRS) score for before and at least 4 weeks after the initiation of aripiprazole monotherapy.
3 A quantitative EEG (qEEG) before starting aripiprazole treatment.
4 Age between 18-65
5 No physical illness.
6 No previous psychotherapeutic interventions.

All the patients were diagnosed by the same psychiatrist (M.K.A). The diagnosis of bipolar disorder was made in the first interview according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatry Association, 2013). Patients with comorbid conditions, such as epilepsy, organic mental disorders, intellectual disability (or mental retardation), neurological diseases, any medical illness, and a history of head injury, were excluded from the study. The remaining 24 BD patient (13 females) aged at 36.75 ± 13 years (range: 20-65 years) were included to the analysis.

2.2. Young mania rating scale (YMRS)

All patients had pre-treatment and post-treatment Young Mania Rating Scale scores. The Young Mania Rating Scale, originally developed by Young and colleagues (1978), is a clinician-rated, semi-structured measurement used in psychiatric practice and research to assess the severity of manic symptoms. The scale consists of 11 items. Each item is scored according to patient's subjective self-evaluation of his or her previous forty-eight hour-status and clinician's observation. The four of the items are scored from 0 (not present) to 4 and the remaining items are rated from 0 to 8. The total YMRS score may range from 0-60. YMRS scores are categorized as follows: remission (0–12), minimal symptoms (13–19), mild symptoms (20–25), moderate symptoms (26-37) and severe symptoms (38–60) (Young et al., 1978). In the present study, the treatment outcome was the change in the Young Mania Scale. At least a 50% reduction in Young Mania Scale was deemed as clinical response.

2.3. Quantitative electroencephalography (QEEG) Recordings

All qEEG data were obtained before initiation of pharmacotherapy in a quiet, dimly lit room. Participants sat calmly with eyes closed during the 7-min recording time. For all, 19 electrodes (FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1, O2, Fz, Cz, and Pz) were placed on the scalp, based on the international 10–20 system. Linked mastoid electrodes (M1-M2) were used for reference during data acquisition. The data-sampling rate was 500 Hz, and the acquired signals were band-pass filtered at 0.15–70 Hz and notch filtered at 50 Hz. Data artifacts were manually eliminated off-line for each participant. After performing Fast Fourier Transform (FFT) analysis, data were averaged across the recording epochs (2 seconds) for each electrode and average absolute power was calculated for each of the following bands: gamma (30–50 Hz), gamma1 (30–35 Hz), gamma2 (35–40 Hz), high gamma (40–50 Hz). Neuroguide Deluxe v.2.5.1 (Applied Neuroscience, Largo, and FL) software was used for qEEG analysis.

2.4. Statistical analysis

Statistical analyses were performed using SPSS (Version 24). Aripiprazole treatment response was taken as independent variable and absolute power of each electrode-band pair was taken as dependent variable. Because of modest sample size, Mann Whitney U test was selected to compare continuous variables (e.g., age and EEG power) between groups. Differences in categorical variables (e.g., gender) were examined with chi-square test. The threshold for statistical significance was 0.05.

3. Results

Fourteen patients with bipolar disorder responded to aripiprazole while 10 patients were identified as non-responders. The groups did not show any difference in terms of age, gender, duration of aripiprazole usage and the Young Mania score measured before the treatment was initiated (Table 1). Difference between response groups were observed in high gamma band at following electrodes: FP1, F3, F4, C3, P4, Pz, O1, F7, F8, T4, and T5 (Table 2). On these electrodes the non-responders group had greater gamma power as compared to the treatment responders.

4. Discussion

The present study showed that BD patients with higher gamma power did not benefit from aripiprazole monotherapy. These findings are consistent with the earlier study suggesting that gamma activity is related to the treatment resistance in bipolar disorder (Tikka et al. 2015). Our findings particularly suggest that gamma activity might be used as a biomarker for predicting treatment resistance to aripiprazole monotherapy, if confirmed by future prospective studies. The incorporation of such biomarker measures to clinical decision making would optimize treatment strategy. Such a treatment approach is consistent with the concept of personalized medicine and could potentially increase treatment success rate, patient adherence and decrease treatment

Table 1
Demographic and clinical characteristics of patients with bipolar disorder.

	Groups	*N*	*M*	*SD*	*p**
Age	Non-responder	10	38,22	11,88	0.585
	Responder	14	36,50	15,80	
	Total	24	36.75	13.09	
Young Mania (pre-treatment)	Non-responder	10	4.00	3.96	0.693
	Responder	14	6.25	8.83	
	Total	24	6.26	7.58	
Duration (weeks)	Non-responder	10	7.55	6.52	0.886
	Responder	14	6.08	4.71	
	Total	24	6.26	4.78	

		Female	Male	Total	
Gender	Non-responder	5	5	10	0.729[a]
	Responder	8	6	14	
	Total	13	11	24	

Note: * $p < .05$, Independent sample Mann-Whitney U test result
[a] Pearson Chi square test result.

Table 2
Pre-treatment High Gamma absolute power difference between treatment responders and non-responders at relevant regions.

QEEG Bands	Response Groups	*N*	*M*	*SD*	*p**
AP Fp1 High Gamma	Non-responders	10	0.053	.062	**0.036**
	Responders	14	0.019	.012	
AP F3 High Gamma	Non-responders	10	0.028	.022	**0.022**
	Responders	14	0.013	.011	
AP F4 High Gamma	Non-responders	10	0.037	0.046	**0.042**
	Responders	14	0.010	0.006	
AP C3 High Gamma	Non-responders	10	0.026	0.017	**0.026**
	Responders	14	0.014	0.017	
AP P4 High Gamma	Non-responders	10	0.039	0.044	**0.022**
	Responders	14	0.012	0.009	
AP Pz High Gamma	Non-responders	10	0.038	0.049	**0.036**
	Responders	14	0.012	0.008	
AP O1 High Gamma	Non-responders	10	0.028	0.019	**0.031**
	Responders	14	0.016	0.017	
AP F7 High Gamma	Non-responders	10	0.034	0.020	**0.019**
	Responders	14	0.016	0.014	
AP F8 High Gamma	Non-responders	10	0.038	0.050	**0.026**
	Responders	14	0.010	0.007	
AP T4 High Gamma	Non-responders	10	0.031	0.047	**0.016**
	Responders	14	0.007	0.006	
AP T5 High Gamma	Non-responders	10	0.021	0.014	**0.036**
	Responders	14	0.012	0.017	

Note: AP: Absolute Power
* $p < 0.05$, Independent Sample Mann-Whitney U Test.

duration and burden (Vogenberg et al. 2010).

Besides having potential to be used to improve treatment quality, the findings showing increased gamma activity have pathophysiological implications. Gamma band is known to be associated with several cognitive and physiological processes including attention, perception, reading, music, and regulation of sleep-wake cycle (D'Onofrio et al. 2015; Fitzgibbon et al. 2004). In patients with BD, abnormal gamma activity was observed particularly in response to the emotional stimuli (Liu et al. 2014). These findings suggest that the association of increased gamma in treatment resistant BD patients could be related to impaired regulation of sleep-wake cycle, which is a well-known feature in bipolar disorder, or to impaired regulation of response to emotional stimuli. These hypotheses should further be tested by future studies. Given the fact that BD is strongly associated with deficits in cognitive functions (Robinson et al., 2006), any marker reflecting cognitive functions is expected to be closely related to therapy response. Since gamma activity is strongly related to cognitive functioning (D'Onofrio et al. 2015; Fitzgibbon et al. 2004), it is also plausible that it will be correlated to treatment resistance.

The main take-home message of this study is that gamma activity can aid a clinician to decide whether the patient would benefit from aripiprazole at the initial stages of treatment. It is not only clinically but is also ethically important for the clinicians to use markers predicting resistance maximally. For instance, one should take the suicide risk into account (Serafini et al.,2017a) in BD as it is the direct cause of mortality in this patient group. However, it is also worthy of mentioning that aripiprazole it is not gold standard in BD treatment currently. Therefore, the clinician should select the aripiprazole cautiously.

The main shortcoming of our study is that it was performed retrospectively with a small sample size. To precisely evaluate the predictive value of parieto-occipital gamma activity, a prospective longitudinal study should be performed. Nevertheless, our findings might be useful for physicians who actively use qEEG as an aid in clinical practice. Management of bipolar disorder is complex and at times very challenging. Input from ancillary measures such as qEEG might be helpful during such difficult decisions. For instance, patients with greater gamma activity might be better candidates for polypharmacy, although such an approach is not recommended by guidelines for the initial pharmacological treatment of patients with bipolar disorder. Finally, as is well known, aripiprazole is a newer treatment option in BD without significant metabolic side effects and mild neuroleptic-induced extrapyramidal symptom profile (Cuomo et al. 2019). This profile makes aripiprazole a more favorable medication for patients with metabolic syndrome and experiencing extrapyramidal side effects as compared to mood stabilizers and other neuroleptics. Despite the small sample size and retrospective nature of the present study, the findings may be useful for identifying patients suitable for this favorable treatment option.

Author disclosure

Role of Funding Sources

The study did not receive any funding.

Contributors

Author 1 and author 5 designed the research and wrote the protocol. Author 3, author 4 and author 5 conducted literature searches and provided summaries of previous research studies. Author 2 conducted the statistical analysis. Author 3 and author 4 wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Author names:
Mehmet Kemal Arıkan, MD, PhD, professor
Mehmet Güven Günver, PhD
Reyhan İlhan, BA
Özden Öksüz, PhD
Barış Metin, Prof., MD, PhD, professor

Acknowledgement

Not Applicable.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association.
Brand, S, Moller, M, Harvey, B., 2015. A Review of Biomarkers in Mood and Psychotic Disorders: A Dissection of Clinical vs. Preclinical Correlates. Curr. Neuropharmacol. 13 (3). Jul 14.
Cuomo, A, Beccarini Crescenzi, B, Goracci, A, Bolognesi, S, Giordano, N, Rossi, R, et al., 2019. Drug safety evaluation of aripiprazole in bipolar disorder. Expert Opin. Drug Saf. 18 (6). Jun 3.
D'Onofrio, S, Kezunovic, N, Hyde, JR, Luster, B, Messias, E, Urbano, FJ, et al., 2015. Modulation of gamma oscillations in the pedunculopontine nucleus by neuronal calcium sensor protein-1: relevance to schizophrenia and bipolar disorder. J. Neurophysiol. 113 (3). Feb 1.
Fitzgibbon, S., Pope, K., Mackenzie, L, Clark, C., Willoughby, J., 2004. Cognitive tasks augment gamma EEG power. Clin. Neurophysiol. 115 (8). Aug.
J. Hui Poon, S, Sim, K, Baldessarini, R., 2015. Pharmacological Approaches for Treatment-resistant Bipolar Disorder Curr. Neuropharmacol. 13 (5). Oct 13.
Kumar, SR, Sinha, VK, Tikka, SK, Goyal, N., 2015. Gamma activity model for treatment-resistant bipolar psychotic mania. Indian J. Pharmacol. 47 (2), 215. Vogenberg FR, Isaacson.
Liu, TY, Chen, YS, Su, TP, Hsieh, JC, Chen, LF., 2014. Abnormal Early Gamma Responses to Emotional Faces Differentiate Unipolar from Bipolar Disorder Patients. Biomed Res. Int. 2014.
Pini, S, de Queiroz, V, Pagnin, D, Pezawas, L, Angst, J, Cassano, GB, et al., 2005. Prevalence and burden of bipolar disorders in European countries. Eur. Neuropsychopharmacol. 15 (4). Aug.

Robinson, L.J., Thompson, J.M., Gallagher, P., Goswami, U., Young, A.H., Ferrier, I.N., Moore, P.B., 2006. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J. Affect. Disord. 93, 105–115. https://doi.org/10.1016/j.jad.2006.02.016.

Rowland, TA, Marwaha, S., 2018. Epidemiology and risk factors for bipolar disorder. Ther. Adv. Psychopharmacol. 8 (9). Sep 26.

Serafini, G., Canepa, G., Adavastro, G., Nebbia, J., Belvederi Murri, M., Erbuto, D., Pocai, B., Fiorillo, A., Pompili, M., Flouri, E., Amore, M., 2017a. The Relationship between Childhood Maltreatment and Non-Suicidal Self-Injury: A Systematic Review. Front. Psychiatry 8. https://doi.org/10.3389/fpsyt.2017.00149.

Serafini, G., Gonda, X., Canepa, G., Pompili, M., Rihmer, Z., Amore, M., Engel-Yeger, B., 2017b. Extreme sensory processing patterns show a complex association with depression, and impulsivity, alexithymia, and hopelessness. J. Affect. Disord. 210, 249–257. https://doi.org/10.1016/j.jad.2016.12.019.

Staudt Hansen, P., Frahm Laursen, M., Grøntved, S., Puggard Vogt Straszek, S., Licht, R. W., Nielsen, R.E., 2019. Increasing mortality gap for patients diagnosed with bipolar disorder-A nationwide study with 20 years of follow-up. Bipolar Disord 21, 270–275. https://doi.org/10.1111/bdi.12684.

Yatham, LN, Kennedy, SH, Parikh, S V, Schaffer, A, Bond, DJ, Frey, BN, et al., 2018. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 20 (2). Mar.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: Reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.