On the Use of Long-Acting Injectable Aripiprazole in the Treatment of Bipolar Disorder I

To the Editor:

The paper "Aripiprazole Long-Acting Injectable for Maintenance Treatment of Bipolar I Disorder in Adults," by Aggarwal et al. (Clin Schizophr Relat Psychoses 2018;11[4]:221-223), raises some important insights on the use of long-acting antipsychotics in bipolar patients. Given the challenges involved in the treatment of bipolar disorder and the significant morbidity associated with recurrent manic episodes—as well as the elevated rates of poor treatment compliance among bipolar patients—any treatment strategies that seem effective in decreasing rates of relapse and improving a patient's prognosis should be more than welcomed. Despite the efficacy and the FDA approval for the use of long-acting risperidone and aripiprazole for the treatment of bipolar disorder, many clinicians are still unfamiliar with the use of those agents in the management of bipolar patients, hence the need for studies reiterating the efficacy and safety of the medication in question in clinical practice.

However, we would like to emphasize some issues. First, the authors do not provide much information as to the clinical background of the subjects who participated in the study. All patients had a diagnosis of bipolar disorder type I but not much is described with regard to their severity. Information as to previous number of episodes and length of illness would help characterize the participants in terms of staging of their bipolar illness (1) and allow inferences as to how the benefit of the medication in question and its efficacy in preventing relapses might vary depending on the severity of their condition.

Second, it would be of interest to include some information as to the patient's lifetime predominant polarity. Despite the acute disruption and psychopathological morbidity associated with manic states, several studies have established that, from a longitudinal perspective, depressive symptoms tend to have a stronger impact on mental well-being and functional status of bipolar patients (2). Since the evidence on the efficacy of aripiprazole in the treatment of bipolar depression is still limited (3) and, as described by the authors, long-acting aripiprazole did not seem to impact the relapsing rate with regard to depressive episodes, a better description of the sample patients' past histories of manic versus depressive symptoms would be of interest, since it would likely affect a clinician's decision as for indicating long-acting aripiprazole for the treatment of bipolar disorder in clinical practice.

Nonetheless, the paper presents interesting findings. Bipolar disorder remains one of the leading worldwide causes of disability, and long-acting antipsychotics undoubtedly have the potential to play an increasing role in the management of this disease.

Conflicts of Interest

Dr. Sanches has previously served on the speakers' bureau for AstraZeneca and has previously received a research grant from Janssen. None of these sources directly supported or influenced this project, and the author did not receive any financial support relevant to this project.

References

1. Berk M, Post R, Ratheesh A, Gliddon E, Singh A, Vieta E, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. World Psychiatry 2017;16(3):236-244.
2. Rosa AR, Reinares M, Michalak EE, Bonnin CM, Sole B, Franco C, et al. Functional impairment and disability across mood states in bipolar disorder. Value Health 2010;13(8):984-988.
3. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord 2013;15(1):1-44.

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Dr. Aggarwal and Colleagues Reply

To the Editor:

We would like to thank Dr. Sanches for his interest in our paper and appreciate his comments regarding the need to have more information about the clinical background of the subjects who participated in the study that was referenced in the paper (1). We agree that a better description of past psychiatric history of predominantly manic versus depressive symptoms would be of interest. However, the referenced study does not clarify clinical background of the participants and, therefore, we are not able to comment on that.

References

1. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psychiatry 2017;78(3):324-331. doi: 10.4088/JCP.16m11201. PubMed PMID: 28146613.

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Neurocryptococcosis in Immunocompetent Patient with Psychosis

To the Editor:

Abstract

Background: The involvement of *Cryptococcus* as an etiological agent in behavioral disorders, such as psychosis, is a rare finding. **Methods:** We report the case of an immunocompetent 20-year-old man with apparent functioning behavior premorbid that had a first-psychotic episode one day after a clinical condition including mild fever, polyarthralgia, headache, fatigue and insomnia; we detected cryptococcal antigen latex and India ink positive for *Cryptococcus neoformans* in lumbar puncture. The psychotic episode responded to antifungal and antipsychotic treatment. **Conclusions:** We emphasize the importance of paying attention to subtle systemic and neurological signs and investigating the general medical condition cause in the case of a first-psychotic episode. **Key Words:** Cryptococcosis, Psychosis, Neurocryptococcosis.

Infectious agents cause only a small proportion of neuropsychiatric manifestations. The involvement of Cryptococcus as causal agent of behavioral disorders, such as psychosis, is rare (1). In a retrospective study involving 142 patients suffering from cryptococcal meningitis, the following neuropsychiatric manifestations were detected: delirium (47%), mania (33%), depression (19%), anxiety (16%), and psychosis (6%). We will relate the case of a patient with acute psychotic symptoms diagnosed with cryptococcal meningitis.

The patient A, a 20-year-old single male, high school freshman, construction worker, and protestant Christian—very involved in his Assemblies of God's church community—was described as an extrovert and as having many friends and acquaintances. He had no prior identifiable mental illness and his family psychiatric history was negative. He was hospitalized in the psychiatric infirmary of UFPE's Clinical Hospital (HC-UFPE). Ten days before admission he presented with mild fever, polyarthralgia, headache, fatigue and insomnia that lasted 4 days, followed by a psychotic state. He was frequently agitated, and attempted suicide once, and was quoted as declaring: "The prophecy is over! I'm a wash-up! Let me kill myself!" "The world is over!" "I'm dead!" We performed a detailed anamnesis. Because the psychotic symptoms became evident after an apparently systemic clinical syndrome, the initial diagnostic hypothesis was a psychotic disorder due to a general medical condition. We began administering risperidone 2 mg and began extensive investigation of a general medical condition as etiology.

Neurological tests, cranial computed tomography, cranial magnetic resonance imaging, HIV, VDRL, hepatitis B and C serology and other routine tests (TSH and free T4, hemogram, fasting glycemia, total cholesterol and fractions, triglycerides, renal function, hepatic function, ionogram) were all within the normal limits. The only test that showed alteration was the lumbar puncture: cryptococcal antigen latex and India ink positive for *Cryptoccocus neoformans*, no visible sporulation. We began treatment of this immunocompetent neurocryptococcosis patient by administering amphotericin B deoxycholate 50 mg IV and fluconazole 400 mg PO. After two weeks, amphotericin was interrupted and a new lumbar puncture had a negative result.

Patient showed poor discourse, little facial expression and affection, bad hygiene, heard voices commanding him to kill himself and felt people touching him. He showed no clinical symptoms of hydrocephalus such as headache or vomiting. We maintained fluconazole and in 5 weeks increased risperidone to 8 mg. Not seeing the desired improvements after 8 weeks, we switched to olanzapine and increased it to 15 mg. After three months, patient was discharged presenting fluid discourse, coherence, enhanced volition, reactive affection and making plans. He was discharged with 15 mg of olanzapine and 400 mg of fluconazole.

Later, he received aftercare at HC-UFPE's walk-in clinic. We suspended the fluconazole after a year. He returned to study and attended church as before; he was dismissed from his previous job and began looking for work; he was hired as security guard temporarily (only for a month) and he was a good employee. However, affection and cognition are visibly compromised: he has difficulty with social interaction because he has become shyer and less talkative; he has more concrete thinking and slower reasoning so he has more difficulty with logic and problem solving.

Without proper treatment, cryptococcal meningitis is invariably fatal, with an 83% mortality rate in patients without neuropsychiatric manifestation and 76% in patients with it. The procedure with India ink and the determination of the cryptococcal antigen still holds a high diagnostic value (2). The detection of the cryptococcal antigen through latex agglutination has a 95% sensibility and 98% specificity and if it persists after two weeks of treatment might suggest therapeutic failure (3). Thus, the case was discussed with the infectious diseases division and the treatment was carried out according to a consensus on cryptococcosis (4).

The existing literature has little information on evidence of the number of cases in which *Cryptococcus* might be involved in psychotic manifestations. Even though diagnosed with cryptococcal meningitis, the condition heavily influenced a first-psychotic episode; thus, we decided to keep the antipsychotic for at least 18 months after clinical improvement as is recommended for a first-psychotic episode of schizophrenia (5).

In some cases, primary psychiatric diagnosis is prematurely affirmed and serious general medical conditions, such as neurological infections, receive less than optimal attention. Cryptococcal infection is of worldwide occurrence; however, studies on the global distribution of *C. neoformans* and *C. gattii* species

show higher prevalence in Africa and Asia, followed by Central and South America (6). Recent studies estimate that there are approximately 10,000 annual cases of cryptococcal meningitis in Latin America (7); *C. gattii* occurs mainly in Peru, Colombia, Argentina, Venezuela and Brazil (4).

In addition, the cases in literature linking cryptococcal meningitis and behavioral disorders, such as psychosis, are rare. As far as we know, this is the first case of neurocryptococcosis in an immunocompetent patient presenting with psychosis reported in Brazil. Patients presenting confusion psychosis in the absence of constitutional symptoms like fever are never suspected of having an infectious etiology. Thus, cryptococcal meningitis was never considered as one of the differential diagnoses in this patient's case. This may cause mortality without a specific definitive source in cases where a more adequate investigation is not performed. Therefore, we emphasize the importance of investigating a general medical condition cause in the case of a first-psychotic episode, especially neurocryptococcosis, mainly so that the medical practitioners in the above mentioned countries may consider this more frequently as a differential diagnosis.

Disclosure

The authors report no conflicts of interest.

References

1. Prakash PY, Sugandhi RP. Neuropsychiatric manifestation of confusional psychosis due to Cryptococcus neoformans var. grubii in an apparently immunocompetent host: a case report. Cases J 2009;2:9084.
2. Ibanez-Valdes L, Foyaca-Sibat H, Mfenyana K, Chandia J, Gonzalez-Aguilera H. Neuropsychiatry manifestations in patients presenting cryptococcal meningitis. The Internet Journal of Neurology 2004;5(1).
3. Kumar A, Gopinath S, Dinesh KR, Karim S. Infectious psychosis: cryptococcal meningitis presenting as a neuropsychiatry disorder. Neurol India 2011;59(6):909-911.
4. Kon AS. [Guidelines in cryptococcosis – 2008]. Revista da Sociedade Brasileira de Medicina Tropical 2008;41(5):524-544, set-out. Spanish.
5. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry 2017;62(9):604-616.
6. Pizani AT, Santos MO. Criptococose em pacientes HIV positivos: revisão sistemática da literatura. Revista Saúde Uni Toledo 2017;1(1):90-106. Spanish.
7. Vidal JE, Boulware DR. Lateral flow assay for cryptococcal antigen: an important advance to improve the continuum of HIV care and reduce cryptococcal meningitis-related mortality. Rev Inst Med Trop Sao Paulo 2015;57 Suppl 19:38-45.

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