Author’s response to reviews

Title: Ginkgo Biloba Induced Mood Dysregulation: A Case Report

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Author’s response to reviews:

Dear Editor and Reviewers,

Thank you for giving us the opportunity to revise our manuscript. We carefully considered all comments offered. The revision, based on the review team’s collective input, includes a number of positive changes. The answers to Reviewer’s comments are shown below. The changes in the revised manuscript are included in this letter. We thank you for the detail and specific comments and hope our revised manuscript will be viewed as much improved.

With kind regards,

Seung S. Rho, MD; Young S. Woo, MD, PhD; Won-Myong Bahk, MD, PhD

Reviewer’s comment

1. This is a case report on an adverse event that is associated with ginkgo biloba, a commonly used dietary supplement for enhancing cognitive function. The case report warrants publication in view of its novelty, but some clarifications of the history are required. First, is the mood dysregulation compatible with hypomania? Please give some examples of the mood symptoms. Are other hypomanic symptoms, decreased need of sleep, overtalkativeness, etc., also present? Please refer to the DSM-5 diagnostic criteria of hypomania.
Answer 1)

Thank you for the detailed review. Ms. J had symptoms such as irritability, difficulty in controlling anger, and psychomotor agitation which we called “mood dysregulation” in the manuscript. According to DSM-5, diagnostic criteria of the hypomanic episode requires more than four symptoms among the following; irritable mood, grandiosity, decreased need for sleep, talkativeness, racing thoughts, distractibility, psychomotor agitation, and hyperactivity. However, the patient only met two symptoms of these criteria and a hypomania diagnosis could not be made. In this respect, we mention each of the specific symptoms (Case presentation section, line 12-13, page 3) and clearly stated that it is not hypomania (Discussion section, line 5-6, page 4) in our manuscript to reduce confusion.

2. How long after using ginkgo biloba does the mood symptom occur?

Answer 2)

Thanks for the comment. Mood symptoms occurred after taking ginkgo biloba for one week on the first use (Case presentation section, line 5, page 3) and about 5 days on the second use (Case presentation section, line 11, page 3).

3. Any reason given by the patient for re-use of ginkgo biloba despite the adverse effects.

Answer 3)

Thank you for the notice. In spite of our instruction not to use ginkgo biloba any more, the patient decided to resume it because of continuing cognitive discomfort such as difficulty in concentration and short-term memory impairment. To avoid confusion, we added some amendments in our manuscript as follows (Case presentation section, line 10-11, page 3);

Nevertheless, one month later, in February 2017, the patient once again reported that she had tried ginkgo biloba against our instructions because of the subjective cognitive discomfort. Nevertheless, one month later, in February 2017, the patient once again reported that she had tried ginkgo biloba against our instructions because of the subjective cognitive discomfort which still remained.
4. Can you provide some examples of the cognitive deficit in Ms. J? Is cognitive test performed?

Answer 4)

Thanks for the comment. Unfortunately, we thought her cognitive discomfort such as difficulty in concentration and short-term memory impairment (Case presentation section, last line, page 2 – first line, page 3), was related to negative or cognitive symptoms of schizophrenia. We added this limitation in our manuscript as follows (Discussion section, line 2-4, page 5);

Another limitation is that we did not perform any cognitive tests as we regarded her concentration and memory discomfort as being due to the cognitive symptoms of schizophrenia.

5. What are the items on PANSS and BPRS Ms. J has scored?

Answer 5)

Thank you for this question. The items on PANSS and BPRS Ms. J scored have been listed below.

# PANSS 40 points total: Somatic concern, Tension, Uncooperativeness, and Poor impulse control=2; Excitement, Anxiety, and Poor attention=3; All the other items=1

# BPRS 4 points total: Anxiety=2; Excitement=2, All the other items=0

We only mentioned total score with the intention of emphasizing Ms. J’s remission state. In this regard, we did not describe these specific sub-score under the apprehension that it might be a side issue.

6. What is the initial presentation of Ms. J at 29 years old? Are there relapses in the past? What are the types of relapse? What kinds of psychotic symptoms Ms. J had in the beginning? Does Ms. J have manic symptoms in the past?

Answer 6)

Thank you for the comment. Amendments have been made to the manuscript as follows follows (Case presentation section, line 19-26, page 2);

Ms. J started her first psychiatric outpatient clinic when she was 29. She showed restricted affect at the time and was experiencing delusion of being controlled with auditory hallucination of a
commanding nature, and was diagnosed as having schizophrenia. Risperidone was prescribed within the range of 2 to 6 mg with favorable response, and her symptoms gradually improved. However, after 2 years of remission periods, she decided on her own to discontinue taking the prescription, and this led to a recurrence of symptoms similar to those occurring at the time of her first episode. From then on, she has taken her prescription consistently and has been in stable condition. The patient has maintained remission with risperidone 2 mg monotherapy. In addition, she has never experienced any kind of mood episode.

(Case presentation section, line 5-6, page 3);

She said that these symptoms were the first she had experienced during her illness.

7. Are there other serious adverse events that are associated with gingko biloba and have been reported in the literature?

Answer 7)

Thank you for the comment. According to literature review, ginkgo biloba is considered fairly safe, as there are neither significant adverse effects, nor known drug interactions. We stated this sentence in our manuscript (Background section, line 12-13, page 2).

8. The paper requires English editing.

Answer 8)

Thanks for the notice. Before the first submission, the paper had undergone English editing service once (HARRISCO Scientific English Research Paper Editing Company, http://en.harrisco.net). Additionally, for this major revision, we have had a second English editing service done. A number of changes are included in this letter. We now accompany the certificate of editing as a PDF file.

Again, we appreciate all your insightful comments. We worked hard to be responsive to them. Thank you for taking the time and energy to help us improve the paper.