Author's response to reviews

Title: Clinical features of delirious mania: a series of five cases and a brief literature review

Authors:

Bo-Shyan Lee (Vc0710@126.com)
Si-Sheng Huang (Vin0710@126.com)
Nan-Ying Chiu (nychiu@126.com)

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Author's response to reviews: see over
Dear Ms. Olino and Professor Greenshaw:

Thank you and your reviewers for your helpful suggestions. After reading the reviewers’ comments, we have made numerous changes and additions to our article, “Clinical features of delirious mania: a series of five cases and a brief literature review.”

We would like to address each of Dr. Karmacharya’s and Dr. Bobo’s concerns.

Thank you so much, and if there are any further questions, please do not hesitate to contact us.

Sincerely,

Nan-Ying Chiu, M.D.
Department of Psychiatry, Lu-Tung Branch of Changhua Christian Hospital
888 Lu-Tung Road, LuKang Town, Changhua County, Taiwan
Tel: 886-4-7789595 ext.1281; Fax: 886-4-7251004
Email: 400842@cch.org.tw

Dr. Karmacharya’s comments (Reviewer 5):

The reviewer was concerned with the organization of the paper, and we have revised several areas to make it clearer that the patients did have some qualities in common.

*We have summarized this in a newly designed Table 1, and also in the text.*

The reviewer noted the differing spellings of MacLean Hospital in the Introduction.

*We have corrected this.*

The reviewer suggested that we use a single term while describing the benzodiazepines. We have done this in the Discussion section, using the single term while giving specific information about individual benzodiazepines in the Case histories.

*As for the concern about concluding that use of benzodiazepines did not lead to resolution of delirium and mania, we rewrote that section to read as follows:*
"High-dose benzodiazepines, especially one-time oral doses of lorazepam (3 mg to 4 mg), often lead to noticeable improvement, but not as reliably as does ECT [1]. In patients 1 and 2, at least one kind of benzodiazepine was given, at most three kinds, all during the course of treatment. From our clinical observation, our use of benzodiazepines didn’t lead to resolution of delirium and mania. But the dose of benzodiazepines in these cases was lower than that suggested by Karmacharya."

The reviewer suggest adding “Result” in the Abstract. So we add it in the rewritten Abstract.

**Dr. Bobo’s comments (Reviewer 6):**

In the Introduction, the reviewer noted the following concerns:

“What exactly is meant by “clarify(ing)” delirious mania, and exactly what “assumptions” are being referred to? I think that the cases do a nice job of illustrating the core features of delirious mania and highlight several challenges in recognizing and treating the syndrome. Perhaps the discussion provided can aid clinicians in recognizing and appropriately treating the syndrome as early as possible, before it progresses to its malignant form.”

*We have rewritten the section in question, so it reads as follows:*

“In an attempt to better describe the course of delirious mania and to provide a clearer picture of this illness, we present a series of 5 patients diagnosed with delirious mania. Our goal was to provide additional information about delirious mania and to illustrate the features of delirious mania and highlight several challenges in recognizing and treating this syndrome.”

*We hope this clarifies our motivation to help other clinicians recognize this illness.*

In the Methods section, the reviewer asked why it was necessary to select only cases with a history of bipolar disorder and whether if patients satisfied diagnostic criteria for mania and delirium simultaneously and no organic cause could be found, would this have been sufficient?

*We deleted the criterion of bipolar disease in the Methods section.*

Case reports: the reviewer asked if in each case we could take extra care to clearly illustrate (perhaps by describing separately) the features of delirium and mania and catatonia when they occurred.

*We have added this information in each Case report, and thank the reviewer for the suggestion.*

Discussion: The reviewer was concerned that the rationale that delirium is the core featured of delirious mania did not have a clear rationale. Thus, if a patient presented with delirium and no mania, one would also not often initially consider the diagnosis of delirious mania. He also asked why it would be more important to identify delirious mania for life-threatening delirium, not
mania. If a patient with mania presents with catatonic signs and vital sign instability in the absence of overt delirium, why would this be of lower priority?

On page 16, second paragraph, we rewrote this section, to include the following sentence: “When only delirium subsided from delirious mania, we supposed that delirious mania was gone while mania remained.”

The reviewer suggested adding more details about the clinical clue of the more rapid onset of mania and psychosis (hours to days) in delirious mania versus bipolar mania (weeks).

We rewrote this section because we lacked sufficient data to support this assumption.

Minor essential revisions:

1. In the Abstract, the reviewer suggested that we consider simply stating that delirious mania is a severe and potentially life-threatening neuropsychiatric syndrome characterized by simultaneous and acute onset of mania and delirium, for which no organic or toxicological cause can be found, and in the Methods section of the Abstract, to simply state that the 5 cases of delirious mania were admitted to the inpatient psychiatric unit, and that a discussion of the cases is provided in the context of a selective review of the clinical literature describing the clinical features and treatment of delirious mania.

We rewrote the Abstract to better reflect this.

2. In the Discussion, the reviewer mentioned that Karmacharya’s paper, which we cited, notes that many signs that distinguish delirious mania from other syndromes are catatonic signs and that catatonic signs can also complicate mania, in the absence of delirium. He also noted that more attention is now paid to catatonia as a potential complication of delirious mania. He questioned whether malignant catatonia, NMS and serotonin syndrome are completely synonymous, and questioned whether NMS and serotonin syndrome were subtypes of malignant catatonia.

Please see two rewritten sections, where these were clarified. One is in the paragraph of “Treatment”.

“In patient 4, delirious mania was accompanied by prominent catatonic signs. This pointed out a dilemma: antipsychotics may be beneficial for delirious mania but they should not be used for catatonia. [31]. In this case, the patient responded to ECT quickly under simultaneous use of antipsychotics. But in patient 1, though catatonic signs were not prominent as in patient 3, it is not known whether antipsychotics were not effective as in other cases, due to presence of catatonia. Though Karmacharya didn’t provide the catatonic signs of his patients, some features may be catatonia-like, for example, extreme psychomotor agitation (pacing, constant
motion), and pouring water (on one’s own head or on the floor). [1] Catatonia may be one possible cause for antipsychotics, especially typical antipsychotics, to be less effective or detrimental in treating delirious mania. This is a question that remains to be answered in future research.”

The other is in the paragraph of “Delirious mania: catatonia? delirium?”

“In Fink’s classification, the worst form of catatonia is malignant catatonia (other subtypes: neuroleptic malignant syndrome and serotonin syndrome). Delirious mania is posited in the milder group, including delirious catatonia and excited catatonia, rather than malignant catatonia. Another classification is the use of excited nonmalignant catatonia for delirious mania. [29] Here the term “delirious catatonia” seems very appropriate because it presents the possibility that delirious mania, which lacks the obvious catatonic signs, and excited catatonia, which lacks sufficient delirious signs (another term like catatonic mania), present two ends of the spectrum of delirious catatonia. In this category, they share the symptoms of excitement, which is similar to mania.”

3. The reviewer suggested deleting Table 3-1.

We agree; we have deleted it.

4. In the Limitations section, the reviewer suggested noting that the cases illustrated challenges to be encountered in real-world care of patients with delirious mania and that the workup and criteria for each case varied.

We added the following sentence to this section:

“The cases illustrate the challenges to be encountered in real-world clinical care of patients with delirious mania; however, the diagnostic workup procedures and criteria selecting and sequencing treatments were not uniform for each case.”