Author's response to reviews

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

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Author's response to reviews:

To: Ms. Catherine Olino  
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From: Dr. Nan-Ying Chiu

Re: Reply to Peer Review Comments on Manuscript 6098822315635124

"Clinical Features of Delirious Mania: A Series of Five Cases and Brief Literature Review"

Dear Ms. Olino:

Thank you very much for the comments from the six reviewers. We appreciate the very helpful comments and suggestions, and have incorporated them into this manuscript. We would like to address the individual comments, by reviewer.

Reviewer 1:

Dr. Fink noted that we sought to answer the suggestion by Fink (1999), Fink & Taylor (2003) and Taylor and Fink (2003) that DM is a syndrome more closely associated with malignant catatonia (MC) than with bipolar disorder (BPD). He noted that we examined only charts of patients with a history of BPD, and no formal tests of catatonia were done, and thus could not contribute to this argument.

Our reply: We agree that lack of examination of catatonia was a limitation of our study. In the Discussion, we attempted to further explain our position including information from the 5 cases, based on Dr. Fink’s view.
The reviewer noted that because patients were treated without a specific protocol for ECT or for medications, we failed to report the impact of polypharmacy, and did not contribute to the role of ECT in DM.

Our reply: We agree that these were limitations of this study.

The reviewer noted that we focused attention on the study by Karmacharya et al (2008) --a chart review for patients with mania and delirium reporting the records of 16 cases. Like the present study, this chart review does not contribute to the questions of the role of BPD in DM nor the efficacy of ECT, nor to the question whether DM is best viewed as a form of BPD or as a type of catatonia.

Our reply: We did a major revision, based on the individual case course, to suggest a hypothesis to explain the relationship between delirious mania as a phenomenon and a manic episode.

The reviewer pointed out that DM is tied to BPD by expectation (that delirious mania must be a form of mania that must be a form of BPD) and by the limitation in the psychiatric classification that classifies BPD as a distinct entity. By assuming that delirious mania is a type of BPD the authors ignore the many cases of DM associated with systemic diseases (e.g., lupus, infections, intoxications).

The reviewer also noted that the number of cases in the literature review fluctuates, and asked that we specify the source of the numbers.

Our reply: We have carefully revised the entire manuscript.

The reviewer pointed out that by restricting our cases samples to patients with a history of BPD the study does not contribute to the arguments that:

a. DM is an acute syndrome not necessarily associated with BPD;

b. That ECT is the effective treatment for DM;

c. That DM is better associated with catatonia, a definable motor dysregulation syndrome not part of schizophrenia, than with MDD.

Our reply: We have made a major revision in the manuscript.

The reviewer noted that the original tables were overwhelming and should be replaced by adding more detail to the case reports.

Our reply: We have deleted three tables (the remaining edited tables are Tables 1 and 2) and we added more description in the case reports.

The reviewer noted a typographical error in the spelling of Bell (not Beck).
Our reply: This has been corrected in the manuscript

The reviewer pointed out duplication in the references, namely that references 18 and 21 were a duplication.

Our reply: We deleted reference 21, and renumbered the references.

The reviewer noted that the discussion of the literature can be better summarized by noting that the cases before 1980 were not tied to BPD.

Our reply: Delirious mania was not closely related with bipolar mania until Bond’s work in 1980. We have revised this accordingly.

Dr. Fink noted that a short chapter in a forthcoming Biography of Catatonia (in preparation) discusses the present position of DM in relation to psychiatric classification. He pointed out a section that might be of interest to us.

Our reply: We thank the reviewer for the suggestion; however, since the section has not yet been published, it is difficult to cite in the current manuscript.

Reviewer 2:

We thank the reviewer for his nice comment about the case report and literature review.

Reviewer 3:

The reviewer recommended a major revision, asking that we state the number of patients excluded for failing to meet one or more criterion.

Our reply: The original chart review was deleted from the manuscript and only 5 cases were discussed thoroughly and individually in the revised manuscript.


Our reply: We added these references.

The reviewer noted that in the Discussion section, we mentioned that “antipsychotics and mood stabilizers alone are less effective in controlling the symptoms of delirious mania.” He also noted that other authors have stated that antipsychotics may indeed be harmful and exacerbate the clinical condition, and
the major treatments appear to be benzodiazepines and ECT, and asked us to comment further on this.

Our reply: We added the following section to the Discussion:

Although traditional antipsychotics were used broadly and successfully to treat delirium [27], some authors warn that with delirious mania, traditional antipsychotics should be avoided. [1, 8] So it is inevitable to suspect that traditional antipsychotics delayed remission of delirious mania or even worsened it at the first admission it for patient 1. At his second admission, use of antipsychotics was limited to new-generation agents, but delirious mania persisted just as in the first episode. New-generation antipsychotics with a mood stabilizer were used without ECT used in patients 2 and 5. Delirium ceased within 1 week of admission in patient 2 and after 2 more weeks in patient 5. The results in these two patients echoed those of some new reports that new-generation antipsychotics may be beneficial for delirious mania [13, 28]. Our findings support Karmacharya and colleagues’ findings that antipsychotics and mood stabilizers alone are less effective in controlling the symptoms of delirious mania.

Reviewer 4:

The reviewer suggested that a brief literature review was not ideal because readers have to analyse reported date to assess whether tabulated data presented do or do not provide any new insights about delirious mania. He suggested that we consider a more thorough literature review to compare and contrast our data and then present any new findings from our five cases.

Our reply: We have added extra details and descriptions in each individual case and suggested the concept of simple delirious mania and delirious mania superimposed on a manic episode.

The reviewer notes that in many cases, the doses of medication, and days on each medication prior to change were not included. He felt this did not allow the readers to follow the treatment decisions and to assess the risk of neuroleptic malignant syndrome or drug toxicity in the differential diagnosis of each case.

Our reply: We thank the reviewer for this helpful comment. We have added this information in the revised manuscript.

The reviewer suggested that we supply the specific details of our literature search, including key words used in the search.

Our reply: In the revised manuscript, we decided to delete the literature review section and instead to focus on a detailed description of the 5 patients.

The reviewer commented that in Case 1, second paragraph, sentence 2: “…he presented with delirium and mania at the same time…” and wondered if we are
implying that the delirium and mania started concurrently or that this was the point along the disease course and make no assumptions about disease course prior to presentation?

Our reply: When this patient was admitted, he obviously had mania, and the mania then was worsening. Before he was admitted, the patient was displaying symptoms that resembled those of disorganized mania.

The reviewer asked what treatment was given when the patient was transferred to another hospital.

Our reply: We have updated this information in the revised manuscript.

The reviewer also asked what medications were given 2 months after discharge?

Our reply: We have updated this information in the revised manuscript.

In Case 2, the reviewer asked several questions; First, in the third sentence, was haloperidol, 2 mg to 5 mg /day needed or scheduled. Was this as needed or scheduled?

Our reply: It was given as needed.

The reviewer also asked for an explanation about the schedule of medication, including the quetiapine dose. He also asked what the full medication list was when the patient was discharged in “partial remission.”

Our reply: We already updated this part in the revised manuscript.

In Case 3, the author had several requests: the doses of bupropion and olanzapine, and paroxetine and lithium. He also asked about the final discharge list of medications.

Our reply: We updated this in the revised manuscript.

The reviewer asked in Case 4, Was the initial mania secondary to the prodrome of the aspiration pneumonia and respiratory failure? The case for delirious mania in this case appears tenuous. He suggested that we consider ruling out delirium due to general medical conditions with catatonic symptoms. He felt this needed more information to clarify the issue.

Our reply: We updated this in the revised manuscript.

In Case 4, Paragraph 3 first sentence: “…aripiprazole 10 to 15mg/day..”. He asked what the dose was here.

Our reply: The dosage was titrated up to control mania symptoms. We updated this in the revised manuscript.
The reviewer had numerous questions about Case 5. Case 5: Paragraph 2, sentence 6: “...left upper weakness, but he totally recovered when he was admitted to the hospital with no exact information of lesion of cerebral infraction.” He felt this sentence was unclear, and asked that we include doses, days on each medication and medication form (e.g., immediate release, extended release) for aripiprazole, paroxetine, valproate and quetiapine. He also asked if the patient’s drug compliance was poor prior to and after the intracranial hemorrhage?

Our reply: We updated this in the revised manuscript.

The reviewer had various comments about the Discussion section:

Have all ages in the same decimal notation: e.g., 38.86 years should be 39 years as all other ages have no decimal notation.

Paragraph 2, last sentence: “this might suggest...for pure delirium”. There is ample literature supporting this. Suggest a broader literature review for an evidence based observation.

Paragraph 3, first sentence: include the references for the four patients noted for other studies.

Paragraph 3, sentence 4: the authors need to cite relevant literature for an evidence based observation.

Paragraph 3, sentence 11: “All these reports seem to support ...reported [4].” It is well reported that the disease course of delirious mania that usually begins with hypomania and progresses to mania and then to delirious mania; thus, speculation on this fact is not instructive.

Paragraph 3, sentence 12: As in the preceding sentence, this sentence can be removed as there is ample literature (using names other than "delirious mania") describing the course of delirious mania both treated and untreated.

Paragraph 4, fist sentence: Without careful documentation of the medication doses, the number of days on each dose, with the lack of washout times between changing multiple doses of medications of questionable strengths, the statement suggesting an absolute rule out of possible NMS would require more information for the reader to comprehend the conclusion.

Our reply: The Discussion section has been completely rewritten, answering these comments.

The reviewer also had comments about specific clinical symptoms, including Paragraph 1, sentence 6: “Some of …distinct symptoms,” where he asked for clarification.
He noted that in Paragraph 2, sentence 5: “…more than the upper limit of the dose…” and asked if we have ruled out a factor of medication toxicity as described by Fink and Taylor? He commented that “Polypharmacy especially with psychiatric medications it is one the primary causes of delirium?”

Our reply: This was deleted.

In Paragraph 2, sentence 6: “Unlike …these symptoms”, the reviewer felt not enough information was provided for the reader.

Our reply: This was deleted.

The reviewer suggested some discretionary revisions in Cases 1 and 4:

The use of lorazepam 4 mg at night as a hypnotic may have muted the mania symptoms based on existing literature findings. This role of lorazepam in treatment is mentioned in the discussion; its role in case outcome may merit additional discussion.

Our reply: We updated this in the revised manuscript.

In Case 3, 4th paragraph, he said having depression emerge during ECT for mania or delirious mania is not uncommon. He asked us to consider some discussion of this with references in the Discussion section.

Our reply: We added the following information in this case in the revised manuscript:

In patient 3, after the fourth ECT, the patient’s orientation improved while his mania shifted to depression. We know ECT could induce mania [Loo 2011]. But there is no case of ECT-induced depression in the literature. We hypothesized that delirious mania and the manic course subsided at the same time, and mood coincidently switched to depression.

The reviewer commented that in Case 4, first sentence paragraph 2: suggest adding …obvious manic and catatonic symptoms of …”. With a 15 year history of bipolar disorder and 4 previous hospitalizations for manic episodes, the risk of delirium of this 50 year old patient is greatly increased due to the brain changes documented for bipolar patients (Psychiatric Annals February 40;2010); i.e., the brain age of this patient is may be equivalent to that of a geriatric person. Thus the risk of delirium due to incipient pneumonia is highly probable. He suggested that one questions that might merit attention, is how vulnerable is the aging bipolar, schizophrenic or schizoaffective disorder patient’s brain to delirium and delirious mania?

Our reply: Patients 3 and 4 had medical illnesses other than BD at admission. In
such cases, it is difficult to make a differential diagnosis of the cause of delirium. The mild inguinal hernia in patient 3 and the resolution of pneumonia in patient 4 may have made them vulnerable to delirium; predisposing factors include advanced age, dementia, and male gender.[21] However, these illnesses had been treated appropriately and presented no worsening signs that would have required more aggressive management. These patients’ obvious manic symptoms made delirious mania the most likely diagnosis. In patient 4, prominent catatonia was seen, and this was recognized as an important sign of delirious mania by Fink. [13]

The reviewer commented about the Discussion, that we had not mentioned the differences in presentation and treatment, using the proposed nosology of Fink and Taylor mentioned in the text, of their cases regarding the differences between non-malignant delirious catatonia versus malignant delirious catatonia (vedi Van Den Eede et al. 2005).

Our reply: We have added the following information to the revised manuscript:

In Fink’s classification, the worst form of catatonia is malignant catatonia (also termed neuroleptic malignant syndrome or serotonin syndrome). Delirious mania is posited in the same subtype as delirious catatonia (delirious mania, excited catatonia), and is described as milder than malignant catatonia. Another classification is the use of excited nonmalignant catatonia for delirious mania. [29] Here we like the term “delirious catatonia” 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. And we agree that delirious catatonia is a nonmalignant syndrome.

Reviewer 5:

Reviewer 5 noted that it is not easy to deduce the clinical course clearly and he felt it was unclear which/if any treatment had salutary or deleterious effects. He also noted that ECT was beneficial, but only two of the five patients had received ECT and one became depressed after ECT. He commented that high-dose benzodiazepines are effective but this does not seem to have been tried in these patients. The authors note "we found no obvious effect of benzodiazepines in our cases" but they do not describe the doses of benzodiazepines used and duration of treatment for these patients. It would also be useful to know if antipsychotics made the symptoms better or worse. Authors state that patient 2 showed weakness and disorientation after starting zuclopenthixol, patient 1 had been put on 15 mg/day of haloperidol but was discharged on the 71st day without full remission and patient 3 had tongue dyskinesia on olanzapine. Did antipsychotics, especially typical antipsychotics, seem to make the clinical picture worse for these patients, as has been suggested in some other studies or did the antipsychotics seem to help?
Our reply: We added the following information to the revised manuscript:

Although traditional antipsychotics were used broadly and successfully to treat delirium [27], some authors warn that with delirious mania, traditional antipsychotics should be avoided. [1, 8] So it is inevitable to suspect that traditional antipsychotics delayed remission of delirious mania or even worsened it at the first admission it for patient 1. At his second admission, use of antipsychotics was limited to new-generation agents, but delirious mania persisted just as in the first episode. New-generation antipsychotics with a mood stabilizer were used without ECT used in patients 2 and 5. Delirium ceased within 1 week of admission in patient 2 and after 2 more weeks in patient 5. The results in these two patients echoed those of some new reports that new-generation antipsychotics may be beneficial for delirious mania [13, 28]. Our findings support Karmacharya and colleagues' findings that antipsychotics and mood stabilizers alone are less effective in controlling the symptoms of delirious mania.

The reviewer then commented that the report is a little difficult to follow at times due to some inconsistencies. In the abstract, authors report that they compared their five patients with fifteen other patients from the literature, and "the course of illness and treatment interventions were compared among all 18 patients", instead of 20 (5+15). But on Table 2, they report 7 episodes in 5 patients in this study, 19 episodes in 11 patients from literature and 16 episodes in 16 patients from another study. He felt this was very confusing.

Our reply: We deleted this part and instead focused on 5 cases.

Reviewer 5 commented that we report that several patients fulfilled the criteria for catatonia. The criteria should be described clearly in the text, i.e. what constitutes fulfilling the criteria. Only one of the five patients (patient 4) appears to have significant catatonic symptoms based on Table 4.

Our reply: We have added the following information in the revised manuscript:

However except for patient 4, catatonia was not very obvious in patient 1 and patient 2. Both patient 1 and patient 2 had excessive motor activity while patient 1 had posturing at the first admission, rigidity of limbs at the second admission, patient 2 having rigidity (though this should have been attributed to medications).

The reviewer noted some factual/typographical errors, including changing “Beck” to “Bell.” In describing Patient 2, he noted that we stated that both dementia and mania were suspected and asked if this should be “delirium and mania were suspected”? Also, in the references, there was a typographic error where MBBS) was listed as part of the title of the paper.

Our reply: These errors have been corrected in the revised manuscript.
Reviewer 6:

The reviewer felt that the cases do not illustrate in enough detail the core clinical features of delirious mania, or explicitly describe the clinical logic applied by the authors when arriving at a diagnosis of delirious mania and selecting specific treatments.

Our reply: We revised the manuscript dramatically by focusing on the description of the five patients.

The reviewer also thought the Discussion section should focus on these clinical issues, using the cases as a platform for discussion, in order to achieve the stated goal of the review--to improve early recognition of delirious mania and facilitate proper treatment.

Our reply: The Discussion section was dramatically revised.

The reviewer pointed out several major revisions, including the classification of delirious mania, noting that throughout the paper, delirious mania is referred to as a severe form of mania. Indeed, some have argued that this is its proper classification. However, the issue is far from resolved. He cautioned against referring to delirious mania as simply a severe form of mania.

Our reply: We thoroughly agreed with the reviewer’s comments and dramatically revised this section of the manuscript.

The reviewer noted that the core features of delirious mania are delirium, mania, and psychosis, with or without catatonia. However, he noted that the only apparent inclusion criteria for the five cases was meeting diagnostic criteria for delirium during the treatment of mood disorders. He asked if one could assume that specific clinical criteria for mania were also applied. If so, what were they?

Our reply: We presented five patients from our clinical practice at our ward. The criteria were used to select them included their past history of bipolar disorder [13], the current manic symptoms, delirious state during the hospitalization period, and no medical cause for delirium except the concurrent mania. Other than this criteria, we had no further criteria.

The reviewer asked if clinical rating scales were used to establish the presence (or absence) of the core features of delirious mania and measure their severity. Bedside clinical rating scales are available for the signs and symptoms of mania, psychosis, catatonia, and delirium. He stated that the scores should be reported and if they weren’t used, this would be a significant limitation that should be discussed.
Our response: Except Young Mania Rating Scale used at the 2nd episode of patient 1, no other clinical rating scale was used. We knew this was the limitation at our article.

The reviewer asked about methods of case report ascertainment and inclusion and noted that information in this section could include databases consulted, date ranges, search terms, and criteria for inclusion.

Our response: This part is deleted in the revised manuscript.

The reviewer had some general comments about the Case Reports:

His form concern was uniform formatting for the cases, adding more specific clinical signs that were manifest during the acute presentation that clearly illustrate the core features of delirious mania--e.g., mania, psychosis, and delirium. He suggested grouping the signs and symptoms of each should be grouped separately to improve clarity. When catatonic features are manifest (Case 4), he suggested they should also be described separately and in detail.

The reviewer indicated that the case reports should include at least some mention of the thought processes by which other elements of the differential diagnosis were considered and then ruled out--thus leading to a diagnosis of delirious mania.

Medication switches were frequent, but the rationale for these changes was not described in all instances. To provide proper guidance to the reader, the rationale behind medication choices and reason(s) for medication changes need to be specified.

Finally, he noted that if there was a delay between discharge and follow-up (after which many patients were noted as being further improved or even remitted), the specific treatments received during that time interval that led to definitive improvement were not described. This information is essential, even if it involved continuation of treatments received at discharge.

Our reply: We addressed each of these comments and all have been added to the revised manuscript.

The reviewer had numerous comments about the Discussion section:

He felt the summary statistics for the demographic characteristics of the 5-member case series was not helpful. This can be deleted.

Our reply: This was revised accordingly.

The reviewer felt it was unclear how differences in the mean age from reported
cases distinguish delirious mania from "pure delirium." He suggested that this part of the discussion should instead focus on clinical features that distinguish delirious mania from "pure delirium" and other items in the differential diagnosis, using the cases as an illustration of these.

Our reply: We deleted this part.

The reviewer questioned how the resolution of delirium before mania and psychosis during ECT indicates that "delirium was most severe at the end of mania." He felt this seemed to suggest that each core feature of delirious mania may respond at different points in time after initiation of ECT, which is itself an important clinical point.

Our reply: We revised this in the Discussion.

Author response: We already did the revision in the Discussion: In this case, we think delirium is the core symptom of delirious mania. When the patient presented only with manic symptoms without delirium, we supposed that delirious mania was not present. This could be only a rough assumption, but it points out that it is more important to identify delirious mania for life-threatening delirium, not mania. In patients 2, 4 and 5, delirious mania responded quickly to effective treatment. This pattern has been found in many case reports, no matter whether the treatment is ECT or just pharmacotherapy. [8, 13-16] It took 2 more months for mania to remit in patient 2 after his delirium disappeared. But on the second admission of patient 1, when mania subsided, delirium persisted. This phenomenon may indicate delirious mania cannot be recognized as the most severe form of mania, as supposed by Carlson and Goodwin.[5] If we viewed delirious mania as a syndrome, as proposed by Fink and Taylor, it would be reasonable because the cause of delirious mania and mania is not the same. [13] Taylor and Fink attributed delirious mania to a form of catatonia because of its good response to ECT and the fact that it was frequently accompanied by catatonic symptoms.[9, 12, 13] They assumed that delirious mania is prone to occur in patients with bipolar disorder (BD), but not solely in BD patients. Following this logic, delirious mania should not be recognized as a specific type of episode in BD. So delirious mania could be superimposed upon BD, and Carlson and Goodwin theorized that one manic episode looked like the most severe form of mania. [5] In such cases, the effective treatment could quickly cure delirious mania but it took longer for mania to remit. In other cases, delirious mania could abruptly appear in stable BP patients. Karmacharya reported one of distinctive symptoms in delirious mania is acute onset (within days) of severe symptoms.

The reviewer wondered about the term, "prodromal manic symptoms" (page 12). He felt this section would be best be devoted to reasons why delirious mania is often missed diagnostically, and what clinicians can do to improve recognition of the syndrome.
Our reply: This part is deleted.

The reviewer stressed the importance of recognizing catatonic signs, threat of progression to malignant catatonia, the need to use extreme caution regarding use of antipsychotic drugs (especially typical neuroleptics), and the sharp contrast between the rapid and often complete treatment response to ECT vs. the poor response to most "traditional" bipolar pharmacotherapies vs. clinical deterioration with typical neuroleptics are not discussed in enough detail, if at all.

Our reply: In the revised manuscript, we added the description of catatonia, ex NMIs, and EPS.

The reviewer asked about limitations to the study.

Our reply: We added this to the manuscript.

The reviewer noted in the background section, that the definition of delirious mania should be provided, since many readers may not be familiar with the syndrome.

Our reply: We added the following to the manuscript:

Background: Little is known about the cause and psychopathology of delirious mania, a type of disorder where delirium and mania occur at the same time.

Reviewer 6 asked us to provide some detail as to how the 15 other cases were identified (e.g., via electronic PubMed search, etc.).

Our reply: This information has been deleted in the revised manuscript.

The reviewer asked use to provide the range of publication dates for the 15 other cases.

Our reply: This information has been deleted in the revised manuscript.

The reviewer noted that in the Conclusion, the statement "delirium is an unusual but potentially life-threatening aspect of severe mania" is confusing. He asked that we consider simply referring to delirious mania as a potentially life-threatening but under-recognized neuropsychiatric syndrome.

Our reply: We agree with the reviewer's comment, and have added this information.

In the Methods section, on page 5, the reviewer asked if the workup was used for ruling out organic causes of delirium standardized across patients? If so, he asked that we specify what types of studies were generally ordered for delirious
patients and, in the case reports, describe what tests were necessary beyond these.

Our reply: We revised the whole manuscript by describing five cases individually. There was no protocol in this study.

In the case reports and clinical signs and symptoms, the reviewer felt it would be helpful to avoid what he describes as vague or non-specific terms such as "inappropriately touched," "mild cortical dysfunction," "loquacious speech" (Case 3--assume this refers to pressured speech), "temperature" (Case 3--assume this refers to fever), "irrelevant speech" (Case 5--unsure exactly what this describes), "feelings he described as an 'earthquake'" (Case 5 --again, unsure what this means clinically), and "...consistent with old brain damage" (Case 5). He suggested that these could be replaced with descriptions of the observed behaviors, or use of more specific medical terms, when applicable.

Our reply: We appreciated these comments and the manuscript was revised accordingly.

The reviewer noted that in Case #2, page 7, it is stated that "both dementia and mania" were suspected. He asked if it were "delirium" that was suspected (not dementia)?

Our reply: The manuscript was revised according to the reviewer’s suggestions.

In Case 3, page 9, the reviewer noted that lithium level is not a hematologic study, and suggested that this be changed to “the lithium level on admission was 0.41 mEq/L.”

Our reply: The manuscript was revised according to the reviewer’s suggestions.

The reviewer noted in Case 4 that echolalia and echopraxia are not manic symptoms. They are, however, important catatonic signs.

Our reply: The manuscript was revised according to the reviewer’s suggestions.

The reviewer asked if in this patient with delirious mania and catatonic signs, were the benzodiazepines initiated to manage catatonia? Was consideration given to holding all antipsychotic drugs given the risk of illness progression (to clinical picture resembling neuroleptic malignant syndrome) in this type of patient? If vital signs were stable and catatonic signs resolved with benzodiazepine treatment, the use of an atypical antipsychotic drug may then be safe.

Our reply: Except for patient 4, who was treated directly with ECT, patient 1 and 2 were just on the borderline of catatonia.

The reviewer was interested in the fact that Patient 4’s fever recurred and
wondered what the cause was.

Our reply: There was no recurrence of fever.

In Case 5, the reviewer was confused by the following sentence: "At age 54, he once had a stroke...with no exact information of lesion of cerebral infarction."

Our reply: We did not have precise information about this patient.

We appreciated the effort that all six reviewers made to improve this manuscript, and hope that we have satisfactorily answered all their questions and concerns. If you should have any additional questions, please feel free to contact me at any time.

Yours sincerely,

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