Reviewer's report

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

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Reviewer: William Bobo

Reviewer's report:

The authors present a small case series and selective literature review to describe the clinical features, course and treatment of delirious mania. Delirious mania is a severe and potentially life-threatening neuropsychiatric syndrome that is robustly responsive to electroconvulsive therapy, but tends to respond less-well to standard pharmacotherapies for bipolar disorder. Some bipolar treatments, such as typical neuroleptics, may result in clinical deterioration. Catatonia is often a prominent illness feature. In spite of its severity, it is often under-recognized. Poor recognition of the syndrome is likely facilitated by lack of consensus as to the proper classification of delirious mania, and lack of formal categorization in the DSM-IV-TR. The most severe forms of delirious mania are medical emergencies.

• This report addresses a topic of clinical importance, and one that would be of interest to the journal readership.
• The most serious limitation is 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.
• In addition, the discussion 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.
• Attention to these major revisions are needed before a recommendation for publication can be provided. Specific additional comments are provided below, which I hope the authors will find useful.

Major Compulsory Revisions:

1. Delirious mania classification: 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. As such, I would caution against referring to delirious mania as simply a severe form of mania.

2. Methods, inclusion of cases:
   (a) The core features of delirious mania are delirium, mania, and psychosis, with or without catatonia. However, the only apparent inclusion criteria for the five
cases was meeting diagnostic criteria for delirium during the treatment of mood disorders. Can one assume that specific clinical criteria for mania were also applied? If so, what were they?

(b) Were clinical rating scales 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. If so, the scores should be reported. If they were not used, this is a significant limitation that should be discussed.

3. Methods of case report ascertainment and inclusion: The method for selecting cases was not specified, nor were the criteria for inclusion/exclusion. Information in this section may include databases consulted, date ranges, search terms, and criteria for inclusion.

4. Case reports, general:
(a) The case reports, which serve as the central feature of the paper, are not uniformly formatted. To improve readability, the order in which information is presented should be essentially the same for each case.

(b) More clinical detail should be provided about 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. The signs and symptoms of each should be grouped separately to improve clarity. When catatonic features are manifest (Case 4), they should also be described separately, and in detail.

(c) 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.

(d) Medication switches were frequent, but the rationale for these changes were 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.

(e) Finally, 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.

5. Discussion:
(a) Reporting summary statistics for the demographic characteristics of the 5-member case series is not helpful. This can be deleted.

(b) It is unclear how differences in the mean age from reported cases distinguish delirious mania from "pure delirium." Indeed, elderly patients may be more prone to delirium for a variety of reasons; however, delirium may still present at any age. 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.
It is also not clear how the resolution of delirium before mania and psychosis during ECT indicates that "delirium was most severe at the end of mania." This simply seems 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.

I am unsure what is meant by the term, "prodromal manic symptoms" (page 12). This section would be best devoted to reasons why delirious mania is often missed diagnostically, and what clinicians can do to improve recognition of the syndrome.

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.

Limitations: Limitations to the authors' report are not provided.

Minor Essential Revisions:

7. Abstract:
(a) The paper should be referred to as a case series;
(b) In the background section, the definition of delirious mania should be provided, since many readers may not be familiar with the syndrome;
(c) Please provide some detail as to how the 15 other cases were identified (e.g., via electronic PubMed search, etc.);
(d) Please also provide the range of publication dates for the 15 other cases;
(e) In the conclusion, the statement "delirium is an unusual but potentially life-threatening aspect of severe mania" is confusing. Please consider simply referring to delirious mania as a potentially life-threatening but under-recognized neuropsychiatric syndrome.

8. Methods, page 5: Was the workup for ruling out organic causes of delirium standardized across patients? If so, please specify what types of studies were generally ordered for delirious patients and, in the case reports, describe what tests were necessary beyond these.

9. Case reports, clinical signs/symptoms: It would be helpful to avoid vague or non-specific terms such as "inappropriately touched" (Case 1--assume that this means hypersexual behavior), "mild cortical dysfunction" (Cases 2 and 3--not sure exactly what this defines), "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). These could be replaced with descriptions of the observed behaviors, or use of more specific
medical terms, when applicable.

10. Case #2, page 7: It is stated that "both dementia and mania" were suspected. Was it "delirium" that was suspected (not dementia)?

11. Case #3, page 9: Lithium level is not a hematological study, in the strictest sense. Consider simply stating that the lithium level on admission was 0.41 mEq/L.

12. Case #4, page 10:
   (a) Echolalia and echopraxia are not manic symptoms. They are, however, important catatonic signs.
   (b) 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.
   (c) In this sense, it is of interest that the patient's fever reoccurred. What was the reason for fever recurrence? Did the fever resolve after a negative workup for infectious cause and a course of ECT? After stopping antipsychotic drug treatment?

13. Case #5, page 11: The following sentence is confusing: "At age 54, he once had a stroke...with no exact information of lesion of cerebral infarction."

Discretionary Revisions:

14. Additional case reports to consider: Depending on inclusion criteria for case reports--

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

In the last five years, I have received research support from Cephalon, Inc., and served on speaker bureaus for Pfizer, Inc., and Janssen Pharmaceutica.