Author's response to reviews

Title: Symptoms of epilepsy and organic brain dysfunctions in patients with acute, brief depression combined with other fluctuating psychiatric symptoms: a controlled study from an acute psychiatric department.

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Author's response to reviews:

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Dear Editor-in-Chief.

MS: 1013573215275868 - "Symptoms of epilepsy and organic brain dysfunctions in patients with acute, brief depression combined with other fluctuating psychiatric symptoms: a controlled study from an acute psychiatric department".

On behalf of the authors, we hereby resubmit the revised version of the above manuscript to be reviewed for publication in BMC Psychiatry.

Thank you very much for the positive response to our paper. We are grateful for several useful questions and suggestions from the reviewers.

First, we need to draw Your attention to the fact that during the revision, we regrettably discovered that two p values have been erroneously calculated. These emerged when wrong data were manually entered into a 2x2 table for statistical calculation. Instead of entering the correct 6 AUDS-patients with previous seizures, and hence, 10 patients without previous seizures, 6 and 16 (total no of patients in group) were entered. The same error was done for patients fulfilling criteria for epilepsy. The new and correct p values are 0.018, not 0.027 and 0.043, not 0.057, respectively. The data presented on EEG activity are correct, but the calculations have been made using the same method as in our previous article, i.e. Fisher Exact test comparing the number of abnormal EEG features.

As a consequence of this unfortunate discovery, we have double-checked and recalculated all the reported data and statistical analyses, and are confident that all numbers and p values are now correctly reported. We have improved Table 2
further by reporting n of each group for calculations in which not all patients were included.

We are rather embarrassed having submitted a paper with such blunt errors and hope that you will still consider the paper to be interesting.

Below, please find our replies to each of the reviewers’ comments.

The main objective of the present study was to investigate clinical signs of organic brain dysfunctions and epilepsy in two groups of patients acutely admitted to a psychiatric acute department suffering from different clinical presentations of depression. The patients in the study group were admitted with brief depressive periods coexisting with other rapidly changing psychiatric symptoms. For the purpose of the present study we call this condition Acute Unstable Depressive Syndrome (AUDS). The control group was composed of sex and age matched patients suffering from a Major Depressive Episode (MDE) (time criterion 2 weeks).

Out of 1038 consecutive patients admitted to a psychiatric acute ward, 16 patients with AUDS and 16 patients with MDE were included in the study. Using standardized instruments and methods we recorded clinical data, EEG and MRI. The main results were that a history of epileptic seizures and pathologic EEG activity was more common in the AUDS group than in the MDE group (seizures, n=6 vs. 0, p=0.018; pathologic EEG activity, n=8 vs. 1, p=0.016). Five patients in the AUDS group were diagnosed as having epilepsy, whereas none of those with MDE had epilepsy (p=0.043). There were no differences between the groups regarding pathological findings in neurological bedside examination and cerebral MRI investigation.

The conclusions are that compared to patients admitted with mood symptoms fulfilling DSM 4 criteria of a major depressive disorder, short-lasting atypical depressive symptoms seem to be associated with a high frequency of epileptic and pathologic EEG activity in patients admitted to psychiatric acute wards.

Studies regarding epilepsy or other organic brain dysfunctions in psychiatric acute departments are sparse in spite a high frequency of co-morbid epilepsy in these clinical settings. Studies on depression with such additional symptoms are rare. Studies on subgroups of depression are sparse and needed, as these patients may need different diagnostic and treatment approaches. We believe our results are new, important and needed.

The results in the present manuscript include all EEGs and MRIs taken in the patients’ clinical histories. The QEEG findings from the actual admittance when the patients were included in the study are published in:

Bjørk MH, Sand T, Bråthen G et al. Quantitative EEG findings in patients with acute brief depression combined with other fluctuating psychiatric symptoms: a controlled study from an acute psychiatric department. BMC Psychiatry 2008; 8: 89
This material has not been previously published, it is not being reviewed for publication elsewhere and it has been read and approved by all authors. In the paper the number of words is 2688 excluding abstract, references and tables. In the structured abstract the number of words is 222. There are two tables.

Yours sincerely

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List of changes in the manuscript "Symptoms of epilepsy and organic brain dysfunctions in patients with acute, brief depression combined with other fluctuating psychiatric symptoms: a controlled study from an acute psychiatric department" by Vaaler et al.

Reviewer 1 (Marianna Mazza).

Reviewers report:

This is a very interesting paper, clear and well-written. Discussion and conclusions are adequately supported by the data. Authors have outlined all limitations of the study.

Reviewer 2 (Daniel Kondziella).

Reviewers report:

Minor essential revisions:

1: Background, page 3. “Most frequent are symptoms [in patients with epilepsy] indicating affective disorders and depression”. Please provide a relevant reference.

2: Results, page 8: The attention given to the neurological data is somewhat scant. Please state explicitly; the kind of seizures that occurred in clinical history and the diagnoses of epilepsy the patients received (primary generalized, simple or complex partial etc); the pathology that was found on the MR of the brain; the clinical findings made during neurological bedside evaluation.

3: Discussion, page 9. “Some patients were observed having brief periods of serious affective symptoms including intense suicidal ideations”. Please specify – how many patients, what other symptoms? Besides, this information belongs to Results, not Discussion.

4: Discussion, page 10. “The present study supports the assumption that
pleomorphic…symptoms are indications of epilepsy or organic brain disorders”. This sentence should probably be somewhat modified; I would suggest “epileptic activity” rather than “epilepsy and organic brain disorders” (see also Discussion, page 9, first paragraph).

5: Discussion, page 12. “Several patients probably fulfilled criteria for inclusion but could not be included due to lack of clinical information at admittance”. Please either delete this passage or specify – roughly how many patients? Two, twenty, hundred? What was the “lack of clinical information” due to?

6: Discussion, page 12/13. “Antiepileptic drugs or benzodiazepines […] probably decreased the pathological findings in EEG recordings […]. Thus less EEG pathology should be expected in the AUDS group, not more”. I do not quite buy this argument. Definitively, patients with epilepsy have a higher rate of pathological EEG activity than a non-epileptic population, regardless the fact that they may receive antiepileptic drugs. (Indeed, this is in line with the results from the AUDS group of the present study.) Besides, antiepileptic drugs themselves such as benzodiazepines can lead to pathological EEG findings; increased beta activity is an example.

7: Discussion, page 11. “The majority of antidepressants are relatively safe in epileptic populations”. This is expressed in a very cautious way. Treatment of depression in patients with epilepsy is indeed of paramount importance since depression is associated with poorer seizure control, and the risk of suicide in patients with epilepsy is greatly increased. Besides, there is growing evidence that many antidepressants rather have anticonvulsant effects (Kondziella, Asztely; Acta Neurol Scand 2009).

8: Some concern is related to the style of the manuscript; large passages are written in a somewhat unfocused manner.

a. Abstract. The abstract should be rewritten. Be more specific; instead of “there were significant differences” and “highest numbers were found in the AUDS group” please state what these differences were and provide the relevant data. Likewise, “fluctuating arrays of other psychiatric symptoms” should either be explained or deleted. The first paragraph of the present review may serve as an inspiration for rewriting the abstract, please see above.

b. Background. Again, please focus on the topic of your study. E.g., the very first sentence (“The psychiatric acute and intensive care units serve a broad spectrum of patients in need of acute care”) has nothing to do with the study’s intention and only serves to distract the reader. The same is true for other passages, including the whole last paragraph on page 4 (“The rate of psychiatric involuntary admissions….organic mental disorders (40%) [19]”). Please delete it.

c. Discussion. Again, please focus on your main findings (1. Patients with acute unstable depressive symptoms have a higher rate of epileptic activity, and 2. standardized psychiatric evaluation enables to select these patients during admission). The Blumer studies and the other literature on the association of epilepsy and depression are very well known. It is unnecessary to review them in such a great detail; a very short overview and some relevant citations seem
enough. Please carefully revise the whole discussion and, once again, be as specific as possible. Terms such as “coexisting fluctuating arrays of other psychiatric symptoms” only confuse the reader. It is better to name these symptoms instead. A native speaker may improve grammar and style of the text.

Answers to Reviewer 2:


2: We have added a paragraph in the Results section reporting the seizure types and syndromes of the patients with epilepsy, the types of pathology found on MR and the results of the clinical neurological examinations.

3: The sentences “Most of the depressive periods in the AUDS group lasted for a few hours to a couple of days. Some patients were observed having brief periods with serious affective symptoms including intense suicidal ideations lasting less than one hour.” have been changed, extended and moved to a new paragraph at the end of the Results section. The new paragraph: “Most of the depressive periods in the AUDS group lasted for a few hours to a couple of days. Five patients (31%) had very brief periods with serious affective symptoms, including intense suicidal ideations, lasting less than one hour. Their affective symptoms were agitation with panic attacks, aggression towards others and suicide attempts.”

4: The sentence is modified with a change from “epilepsy and organic brain dysfunctions” to “epileptic activity”.

5: The passage is deleted.

6: The last two sentences in the paragraph are changed to “These medications may have decreased the pathological findings in EEG recordings and stabilised clinical symptoms. Thus, potential EEG pathology may have been masked to a greater extent in the AUDS group than in the MDE group”.

7: The sentence has been changed to “The majority of antidepressants do not reduce the seizure threshold, and there is growing evidence that many antidepressants have anticonvulsant effects [25].” The ref [25] is new.


8:

a: Abstract.

The Abstract is rewritten according to the first paragraph of the review from Reviewer 2.

b: Background.
The first two sentences are changed from “The psychiatric acute and intensive care units serve a broad spectrum of patients in need of acute care [1]. A limited number presents with brief depressive periods accompanied with rapidly changing psychiatric symptoms”, to “In psychiatric acute and intensive care units a limited number of patients presents with brief depressive periods accompanied by rapidly changing psychiatric symptoms.” Reference [1] is deleted.

The whole last paragraph on page 4 is deleted. References [17-19] are deleted.

In the first paragraph on page 4 the following sentences are deleted: “In the classification of epileptic, interictal psychiatric disorders, Blumer proposed a definition of interictal dysphoric disorders [13]. These affective disorders tend to be intermittent and brief, lasting from few hours to two days. In a systematic study of post-ictal depression Kanner et al. found that the patients estimated a median duration of 24 hours in two-thirds of post-ictal depressive symptoms [8]”.

c: Discussion.

The second sentence in the first paragraph is changed from “The data indicates that patients presenting brief depressive periods and coexisting fluctuating arrays of other psychiatric symptoms, have organic brain dysfunctions or seizures in clinical history more often than patients with major depressive episodes”, to “Our results indicate that patients presenting with brief depressive periods and coexisting fluctuating arrays of other psychiatric symptoms like psychosis, panic or mania, have epileptic activity more often than patients with pure major depressive episodes.”

The second and third paragraphs of the discussion are deleted. Refs [26-27] are deleted. There is a rewritten second paragraph: “The typical contemporary psychiatric acute department patient often presents in severe crisis, complicated by substance abuse, polypharmacy, behavioural dyscontrol and multiple Axis 1 diagnoses [28]. The AUDS group patients differ from these typical patients by presenting rapidly changing different clusters of symptoms and having short duration of the depressive episodes. A psychiatric clinical evaluation at admittance based on these clinical aspects could enable the clinician to detect patients with increased possibility of having epileptic activity. This is important information when deciding which drugs to use to rapidly tranquilize the patient. An antiepileptic mood stabilizer or a benzodiazepine would be safe regarding the possibility of lowering the seizure threshold.”

The paragraph “Patients with idiopathic …sub-populations of depressive patients with more neurological soft-signs” is deleted. Ref 29 is deleted.

First paragraph page 12: The sentences “In acute wards patients often present with multiple symptoms, challenging behaviour, sparse clinical information and no definite psychiatric or somatic diagnosis. Acute treatment is aimed at amelioration of symptoms and rapid control of behaviour” are deleted.

Deleted references:
Reviewer 3 (Petr Bob).

Reviewers report:

“The manuscript addresses interesting topic with very important consequences for clinical practice which is worthy of publication but certain points of its presentation need revision. It could be improved by more comprehensive description of methods used in clinical investigations including psychometric measures. Also a more detailed information about patients recruitment would improve credibility of this clinical study.”

Answers to Reviewer 3:

Assessments.

Regarding methods used in clinical investigations:

The two paragraphs page 7 have been changed and extended from

“The patients had three 30 minutes eyes closed EEG-videometry recordings at day 2, day 4-5 and day 8-10 after admittance. They were all done at the same time of the day (+/-1. 5 hours). All patients had an MRI-scan.

Finally after being discharged from the psychiatric acute ward, the patients were referred to an experienced consultant in Neurology (GB) who had access to all EEG and MRI results in clinical history, but was blinded for the grouping of the patients. The neurologist assessed various signs of organic brain pathology from the clinical examination, EEG or MRI examinations”, to

“The patients had three 30 minutes eyes closed EEG-videometry recordings at day 2, day 4-5 and day 8-10 after admittance. The details of the methods for the EEG recordings and quantitative EEG (QEEG) results are published previously [22]. All patients had an MRI-scan with examinations performed at 1.5T or 3T magnetic field strength. The image protocols consisted of at least sagittal T1-weighted images, axial T2-weighted images, coronal FLAIR images and axial diffusion weighted images. In some cases an additional axial FLAIR-sequence was added.

Finally after being discharged from the psychiatric acute ward, the patients were referred to an experienced consultant in Neurology (GB) who had access to both EEG and MRI results from the present admission as well as all other EEGs and MRIs in the medical records. The neurologist was blinded for the grouping of the patients. He assessed various signs of organic brain pathology from the clinical examination, EEG or MRI examinations.”

The reference [22] is new:

symptoms: a controlled study from an acute psychiatric department. BMC Psychiatry 2008; 8:89.

Regarding methods used..psychometric measures:

A new sentence is inserted: “The AUDIT and SCID-1 were applied as soon as the patients were able to co-operate.”

Regarding the Methods section; more detailed information about patients recruitment:

The first paragraph is extended with the following sentences: “Norwegian acute psychiatric services are public and available to everyone. All the patients in the catchment area are admitted to this department. Acute admissions to other psychiatric hospitals occur only if inhabitants temporarily reside outside of the catchment area when the need for acute admittance arises”.

BioMed Central Editorial Comment:

“We note that this is a follow up to your previous publication: http://www.biomedcentral.com/1471-244X/8/89. Can we ask you to please ensure this article is discussed and cited in the revised version of the manuscript, and that you ensure that the novel aspects of the current work are discussed in comparison to the data reported in your previous report.”

Answers to BioMed Central Editorial Comments.

Please see our reply to Reviewer 3, Regarding methods used in clinical investigations.

We have cited the previous publication [Bjørk et al].