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Care and Prudence as Main Directive in Clinical Research on Neurosurgical Intervention for Schizophrenia

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The paper ‘Long-term follow-up of MRI-guided bilateral anterior capsulotomy in patients with refractory schizophrenia’ by Liu et al. [1] reports the effective use of capsulotomy to treat 116 otherwise refractory schizophrenia patients in China. It concludes a response rate of 74% with very few permanent adverse events, which in our opinion is a very impressive clinical result, considering the severity and the complexity of the disorder in this patient group. Overall, the clinical trial was well designed, the paper was informative, and we appreciate the efforts of the authors to publish their results. But since a clinical trial with such a large number of patients may have substantial impact on clinical practice globally, we feel some comments are necessary regarding the sample size, the informed consent procedure, the evaluation scales and the legal aspect of this procedure.

This is a clinical trial investigating an invasive brain surgery for a very severe psychiatric disorder, and according to the authors, this is the first of its kind. Given its uncertainty, risk, controversy and inherent limitations (e.g. lack of control group), is it necessary to include a relatively large number of patients in the early investigational stage of this treatment? For example, almost half of the patients could not give informed consent themselves. Why include those patients when the rest of the patients (≥ 50) were sufficient? It would be most useful (and ethically justified) to see a power calculation, based on an estimated effect size (e.g. taken from the study of Jimenez et al. [2]) to determine the size of the sample needed to demonstrate safety and efficacy.

The reported scores on the Positive and Negative Syndrome Scale (PANSS) suggest that alternative versions from the questionnaires commonly used in schizophrenia studies were used. This way, results are not easy to interpret or to be compared to other outcome studies in schizophrenia. Typically the PANSS is a 30-item 7-point (1–7) rating scale [3], which amalgamated the 18-item Brief Psychiatric Rating Scale (BPRS) and the 12 items from the Psychopathology Rating Schedule [4]. Since BPRS scores are reported separately, this suggests that only subscales for positive and negative effect are reported, e.g. the PANSS-positive scale and the PANSS-negative scale both have 7 items, scored from 1 to 7. Therefore, scores should be between 7 and 49 for each subscale.

However, the reported scores after surgery are 6.86 ± 8.12 for the positive scale, which seems unlikely.

The same is true for the BPRS: the authors mention the use of the 18-item form (scores 1–7) in the method section (see inclusion criteria [1]), so the total score should range from 18 to 126. Table 2 mentions a mean score of 14.46 ± 13.78 after 3 weeks, and one of 14.75 ± 13.21 after 2 years. These numbers seem inconsistent with the scoring system mentioned.

We assume the primary end point of this trial is the Clinical Global Impression (CGI) Improvement rating scale [5]. In the inclusion criteria [1], the authors mention a CGI > 4 , without further explanation. We assume they mean the CGI Severity score here and use the 7-point scoring system. The authors seemed to have modified the CGI Improvement rating scale and changed it from a 7-point to a 5-point rating scale. Was there any particular reason to do so? Patients were evaluated at baseline, and 3 weeks and 24 months postoperatively. Assuming patients came from all over China, was the score after 3 weeks taken after 3 weeks of hospitalization in a ward? The second and third evaluations were almost 2 years apart. Was the CGI Improvement rating scale an ideal primary end point scale to use with such a long evaluation interval?

To the best of our knowledge, the Chinese government already banned the use of neurosurgery for schizophrenia in 2008 [6]. Has this regulation been changed recently? The Chinese government also stated that all clinical trials ought to be provided to patients free of charge, but we did not see any acknowledged partner/sponsor.

These comments are in no way questioning the validity of the work or its importance to others in the field. On the contrary, we feel that the work of Liu et al. is of great significance in the field of neurosurgery for psychiatric disorders.

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