Encephalitis and psychosis

Barry et al reported four cases of anti-N-methyl-D-aspartate (NMDA) receptor antibody encephalitis that presented psychiatrically.1 This report was welcome in highlighting the importance of immunologically mediated encephalitides (or synaptopathies), both primary autoimmune and paraneoplastic, that has emerged over recent years. However, two points are worthy of emphasis.

First, the aetiological association of anti-NMDA receptor antibody encephalitis with ovarian neoplasms was perhaps understated in the paper. In a large study by Dalmau et al, around 50% of cases were associated with ovarian neoplasms and 80% of such patients improved following tumour removal and first-line immunotherapy, whereas only 48% of patients without an identified tumour responded as well to first-line immunotherapy.2 Therefore, the identification and resection of ovarian tumours in patients with this syndrome is a primary concern.

Second, Barry et al conclude that it is important to consider anti-NMDA receptor antibody encephalitis in new-onset psychosis associated with catatonia, seizures and dyskinesia, and that it is unclear whether there is a purely psychiatric presentation. Zandi et al explored this question prospectively in 46 unselected patients with new-onset psychosis, finding anti-NMDA receptor antibodies in 2 patients.3 It was also found that there were no clinical features that differentiated between antibody positive and negative patients. Also of note, this study identified one patient positive for anti-voltage-gated potassium channel antibodies (probably, in fact, anti-leucine-rich, glioma inactivated 1 (LGI1)). It is recognised that psychosis may be a feature of autoimmune encephalitides associated with serum antibodies against a number of proteins, including LGI1 and glutamic acid decarboxylase. Further psychiatric studies are required to determine whether a screen for antibodies associated with encephalitis should be routine in new-onset psychosis.

Authors’ reply: We thank Dr Moran for highlighting the importance of immunologically mediated encephalitis when considering differential diagnoses for atypical psychosis. Dr Moran suggests that the aetiological association of anti-NMDA receptor encephalitis with ovarian neoplasms, in particular teratomas, was perhaps understated in our case series of four patients, where we reported ovarian pathology (a dermoid cyst) in one patient.1 By contrast, Dalmau et al’s original series of 100 cases identified ovarian teratomas in 54 of the 58 cases with ovarian pathology and early removal of such tumours was associated with better outcomes.2 However, more recent studies have not observed such high rates of ovarian pathology.3,4 In a series of 44 patients with anti-NMDA receptor encephalitis, Irani and colleagues found tumours in 9 patients of which 8 cases were ovarian teratomas. Furthermore, 25% of cases overall were male. In keeping with Dalmau and colleagues, the identification and removal of an ovarian tumour was associated with a better outcome, although the best outcome was predicted by adequate immunotherapy during initial illness.4

As noted previously, it is still unclear whether there is a purely psychiatric presentation to this disorder. However, the constellation of symptoms including some or all of catatonia, dyskinesias and seizures with psychosis certainly warrants anti-NMDA receptor antibody testing. We agree with Dr Moran that future studies are required to determine whether routine screening for NMDA receptor antibodies is indicated for atypical presentations, treatment-resistant cases and first-onset psychosis.


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2012 and still no Holy Grail

Allan and colleagues provided a helpful reappraisal of the use of neurostimulatory treatments for depressive illness.5 In their words, the Holy Grail of treatment would be one as effective as electroconvulsive therapy (ECT), but better tolerated and ideally without the need for general anaesthesia. They concluded that ECT has not yet been supplanted, but we wonder whether the authors were aware of how pertinent this observation is for the year 2012.

Electroconvulsive therapy may not be in use in England by the fiscal year 2011–12. Practitioners in ECT will have seen the graph to support this suggestion at various educational events in recent years. It is based on an extrapolation of data that used to be collected by the Department of Health in quarterly surveys of the number of ECT treatments administered in England. The last two surveys were in the fourth quarter of 1998–99, and the fourth
quarter of 2001–02. The estimated annual use fell from about 66000 to 51 000 treatments; if this decline in ECT use continued at the same rate, then the straight line extrapolated from the last data point would reach zero by the year 2011–12. There has never been another national survey. A partial survey of English ECT clinics in the first quarter of 2006 suggested a further fall, to only about 27 000, which was in line with the extrapolation. The re-appraisal prompted us to review the rate of ECT usage in our clinic since 2006.

The rates of ECT usage in 2006 and 2011 were almost identical, that is, 0.82 and 0.83 individual treated patients per 10 000 population in the City of Edinburgh. Likewise, the rates in the intervening years were also almost identical. We therefore conclude, at least for Edinburgh, that the rate of ECT use has been stable for the past 6 years.

The electronic data collection system in our ECT clinic was updated at the end of 2004, and included a record of the primary psychiatric diagnosis of referred patients. The number of referred patients diagnosed with a severe depressive episode (both with and without psychotic features) varied little in these 6 years, from 23 to 28 patients. This gave a crude referral rate of 25 patients with severe depression per year per total population of 500 000.

If we are treating just as many patients with severe depression as 5 or 6 years ago, then this must continue to be resourced. It is not just ECT practitioners that have heard the suggestion about the demise of ECT. Senior managers locally have expressed surprise to hear that there is still a need for the ECT clinic at the Royal Edinburgh Hospital. This concerned us because when the availability of ECT was reduced in Glasgow, ECT use fell. The search for the Holy Grail is laudable, but patients with severe depression still need access to ECT.

Methodological discrepancies in the update of a meta-analysis

Leichsenring & Rabung reported that long-term psychodynamic psychotherapy (LTPP) is superior to less intensive forms of psychotherapy in complex mental disorders. Based on 10 trials, they found an overall effect size (ES) of 0.55. We found several methodological discrepancies in their study.

First, it seems surprising that the Q-test indicated no significant unexplained variance, as the between-group effect size of one of the primary studies was quite outstanding in significant unexplained variance, as the between-group effect size found a significant unexplained variance (only about 27 000, which was in line with the extrapolation. After removing the outlying study, there was no significant unexplained variance ($Q = 11.56$, d.f. = 8, $P = 0.172$).

Second, we calculated the fail-safe $N$ according to Rosenthal; non-published studies with an effect size of 0 had to be included in the analysis to change the results of the meta-analysis ($ES = 0.44$) from significant to non-significant ($ES < 0.16$). As 16 is below 55 ($5K + 10$), the effect cannot be regarded as robust.

Last, to gain better insight into the interpretation of the overall effect size as small, medium or large, we calculated a Bayesian meta-analysis following Higgins et al's methodology. The Bayesian analysis essentially replicated the findings of our random effects meta-analysis. In addition, we found the probability of the overall effect size to be small (ES < 0.5) at 72.5%. Thus, in contrast to Leichsenring & Rabung, we found that the overall effect size was small rather than medium or large.

Therefore, we would greatly appreciate caution against a conclusion that the overall effectiveness of LTPP for treating complex mental disorders should now be considered as definitely proven.


Author’s reply: When trying to replicate some results of our meta-analysis, Kliem and colleagues reported some methodological discrepancies. These discrepancies, however, are due to modifications in their statistical approach as compared with the one we originally reported.

First, in contrast to our results, Kliem et al reported significant heterogeneity between studies for overall outcome as indicated by the Q statistic. As stated in our meta-analysis, we had aggregated the effect size estimates across studies, adopting a random effects model, which is more appropriate than a fixed effects model if the aim is to make inferences beyond the observed sample of studies. Applying a random effects model, the aggregated effect size for overall outcome was 0.54, and heterogeneity was not significant ($Q = 11.72$, $P = 0.23$, $I^2 = 23$). Thus, there was no need for an additional outlier analyses or for the exclusion of any study. As Rosenthal’s fail-safe $N$ was 66, which is above 60 ($5K + 10$), the effect can be regarded as robust. Kliem et al, however, apparently applied the fixed effects model to test for heterogeneity. The use of a fixed effects model, however, addresses another research question and consequently yields different results.


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Furthermore, Kliem et al reported a larger confidence interval for the overall effect size. The confidence interval that they calculated corresponds well to the respective interval that we reported in Table 1, which was 0.26–0.83. A narrower confidence interval, however, was erroneously reported by us in the forest plot owing to a transcription error (Fig. 2, 95% CI 0.41–0.67) – see correction.

Second, after excluding the study by Bateman & Fonagy, which they regarded as an outlier, Kliem et al reported a fail-safe N of 16 unpublished studies with an effect size of 0, which would need to be added in the meta-analysis to change the result from significant to non-significant. However, we could not replicate these findings. After excluding the study by Bateman & Fonagy, we found a fail-safe N of 69, which is above 55 (5K + 10), again indicating that the effect is robust. Apparently, Kliem et al erroneously did not calculate a fail-safe N according to Rosenthal but according to Orwin’s method. Consequently, they did not assess how many studies with ES = 0 had to be included to change the result from significant to non-significant but to ‘not significantly different from 0.16’ – an irrelevant result.

Third, results of Bayesian meta-analyses depend largely on the specification of prior assumptions on the treatment effect and between-trial variance. Since Kliem et al did not provide any information about the assumptions of their analyses, it is impossible to interpret the presented result reasonably.

In summary, we could not confirm the discrepancies reported by Kliem et al. We did not find substantial heterogeneity or any cogent indication of publication bias. The effect in favour of long-term psychodynamic psychotherapy was confirmed as robust. Instead, we could show that most of those ‘discrepancies’ seem to be based on differing methodological approaches.

Identifying responders in randomised controlled trials for depression

The usefulness of antidepressants in patients with mild or moderate depression has been questioned and therefore Thase et al re-analysed randomised controlled trial (RCT) data for escitalopram. They calculated that a subgroup of patients (14%) with mild or moderate depression did respond to treatment and not to placebo, but that the subgroup of patients with severe depression who responded to treatment was larger (23%).

The findings from Thase et al illustrate what is known from the philosophy of science about RCTs: if T causes O in a population, this only implies that T causes O in at least some members of that population. Reporting average results can be misleading if the population is not causally homogeneous.

Ideally, one should try to identify the specific subgroup of responders. The authors could consider analysing their data further by looking at demographic factors such as age, because younger people are less likely to respond, and the presence of particular symptoms such as anxiety, which might adversely influence outcome as well, if these data are available. However, it is unlikely that one can identify the subgroups of responders with 100% accuracy with these additional data.

More generally, Thase et al’s results show that by reporting average results, important findings from RCTs might be missed. Reporting binary outcomes such as number or percentage of patients improved or in remission should be encouraged in psychiatric research, even if the primary outcome variable is considered to be a continuous interval variable. This applies to all RCTs with non-homogeneous populations. Unfortunately, CONSORT requirements do not make this compulsory at the moment.


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Corrections

Long-term psychodynamic psychotherapy in complex mental disorders: update of a meta-analysis. BJP, 199, 15–22. Figure 2 (p. 19): total effect size CI should read 0.26 to 0.83.

Predicting the development of schizophrenia: authors’ reply (letter). BJP, 200, 255. Jeffer Chuma is Clinical Studies Officer with NIHR Mental Health Research Network (North West Hub), and Prem Mahadun is Consultant Psychiatrist with the Trafford Crisis Resolution and Home Treatment Team.

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