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Contents

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 synaptopthies), 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 pure 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.

1 Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, et al. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. *Br J Psychiatry* 2011; **199**: 508–9.

2 Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; **10**: 63–74.

3 Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol* 2011; **258**: 686–8.

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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,[2] 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.

1 Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, et al. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. *Br J Psychiatry* 2011; **199**: 508–9.

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3 Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009; **66**: 11–8.

4 Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; **133**(Pt 6): 1655–67.

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2012 and still no Holy Grail

Allan and colleagues provided a helpful reappraisal on the use of neurostimulatory treatments for depressive illness.[1] 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.[2] The estimated annual use fell from about 66 000 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.[3] 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.[4] The search for the Holy Grail is laudable, but patients with severe depression still need access to ECT.

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Methodological discrepancies in the update of a meta-analysis

Leichsenring & Rabung[1] 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[2] (ES = 1.76) is quite outstanding in Fig. 2. To shed light on this issue, we recalculated the overall effect size using a random effects meta-analysis based on the values from Fig. 2. Our meta-analysis replicated Leichsenring & Rabung[1] in the main. In contrast to Leichsenring & Rabung however, we found a significant unexplained variance ($Q = 25.33$, d.f. = 9, $P = 0.003$) and a larger overall confidence interval of 0.29–0.82 (in contrast to 0.41–0.67 as reported by Leichsenring & Rabung). Additionally, computing an outlier analysis, a significant outlying study effect size was found ($P < 0.001$). Including the moderator considering the impact of this study yields an effect size of 0.44 (95% CI 0.27–0.61, $P < 0.001$). The moderator effect, interpreted as the difference between the effect of the outlying study and the grand mean, was 1.32 (95% CI 0.57–2.07, $P < 0.001$). 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;[3] 16 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.[4] 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,[1] 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.

1 Leichsenring F, Rabung S. Long-term psychodynamic psychotherapy in complex mental disorders: update of a meta-analysis. *Br J Psychiatry* 2011; **199**: 15–22.

2 Bateman A, Fonagy P. The effectiveness of partial hospitalization in the treatment of borderline personality disorder, a randomized controlled trial. *Am J Psychiatry* 1999; **156**: 1563–9.

3 Rosenthal R. The file drawer problem and tolerance for null results. *Psychol Bull* 1979; **86**: 638–41.

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Author's reply: When trying to replicate some results of our meta-analysis,[1] Kliem and colleagues reported some methodological discrepancies.[2] 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,[1] 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.[1,2] 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.