BJPsych | The British Journal of Psychiatry (2019) 214, 305–307.

Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

Contents

Response to the article entitled 'Mood stabilisers and risk of stroke in bipolar disorder'

We read with great interest the article 'Mood stabilisers and risk of stroke in bipolar disorder' by Chen *et al*, published in this esteemed journal.[1] The authors have assessed the association between mood stabilisers and risk of stroke in patients with bipolar disorder. They have addressed multiple potential confounders such as age, gender, physical illness and concomitant medication. However, we would like to discuss some important factors that could have influenced the study findings.

First, the study did not consider the role of psychiatric comorbidity. Only admission for bipolar disorder was taken into account. Certain psychiatric illnesses are common in patients with bipolar disorder and are noted to be risk factors for stroke as well. For example, the lifetime prevalence of anxiety disorder in bipolar disorder has been found to be 42.7%.[2] Further, anxiety disorders have been associated with a 24% increased risk of stroke compared with the general population.[3]

Second, the role of psychosocial factors in stroke is not addressed. It is important to note that bipolar disorder is associated with several psychosocial factors and a recent meta-analysis mentions that the risk of stroke is increased by psychological, vocational and interpersonal factors by almost 39%, 35% and 16%, respectively.[4]

Third, bipolar disorder is associated with high rates of non-adherence to medication. As the study focuses on the association between mood stabiliser and bipolar disorder, the adherence to mood stabilisers is an important variable to be considered. This point is worth highlighting as the mean prevalence of non-adherence to medication has been found to range from 41.5% to 43%.[5]

Fourth, the role of oral contraceptive pills has not been discussed. The increased risk of stroke with oral contraceptives is well-known. About 42.7% of participants are women. Oral contraceptives are used commonly by women for contraception as well as prescribed for polycystic ovarian syndrome, which is not uncommonly seen with use of valproate.

Fifth the comorbidity of seizure disorder has not been considered. This is important to address mainly for two reasons. Both valproate and carbamazepine are prescribed in patients with seizure disorder or epilepsy as well as in patients with bipolar disorder. Further, literature exists that late-onset epilepsy has been associated with increased risk of stroke.[6] This is a point to be noted as almost 61% of the participants were recruited when more than 45 years old.

Finally, the term 'any mood stabiliser' is not clearly defined. For example, the number of patients on any mood stabiliser during the case period is 212. However, the sum of patients as per numbers given separately for carbamazepine (35), valproic acid (118), lithium (62) and lamotrigine (18) is 233.

References

1 Chen PH, Tsai SY, Pan CH, Chang CK, Su SS, Chen CC, et al. Mood stabilisers and risk of stroke in bipolar disorder. *Br J Psychiatry* 2019; **214**: 305.

2 Nabavi B, Mitchell AJ, Nutt D. A lifetime prevalence of comorbidity between bipolar affective disorder and anxiety disorders: a meta-analysis of 52 interview-based studies of psychiatric population. *EBioMedicine* 2015; **2**:1405–19.

3 Perez-Pinar M, Ayerbe L, González E, Mathur R, Foguet-Boreu Q, Ayis S. Anxiety disorders and risk of stroke: a systematic review and meta-analysis. *Euro Psychiatry* 2017; **41**: 102–8.

4 Lightbody CE, Clegg A, Patel K, Lucas JC, Storey H, Hackett ML, et al. Systematic review and meta-analysis of psychosocial risk factors for stroke. *Semin Neurol* 2017; **37**: 294–306.

5 Chakrabarti S. Medication non-adherence in bipolar disorder: review of rates, demographic and clinical predictors. *World J Metaanal* 2017; **5**: 103–23.

6 Ben-Menachem E. Epilepsy as a warning sign for stroke. *Epilepsy Curr* 2005; **5**: 42–3.

Pooja Patnaik Kuppili, Senior Resident, All India Institute of Medical Sciences, India; **Kartik Singhai**, Junior Resident, All India Institute of Medical Sciences, India; **Naresh Nebhinani**, Associate Professor, All India Institute of Medical Sciences, India. Email: poojapatnaik.aiims@gmail.com.

doi:10.1192/bjp.2019.63

Author's reply

We thank Kuppili, Singhai and Nebhinani for their recent comments on our article 'Mood stabilisers and risk of stroke with bipolar disorder'.[1] Their comments drew attention to several confounding factors that could have influenced our study findings.

The association between anxiety disorders and risk of stroke has recently received increased attention because of its high prevalence in bipolar disorder.[2] In addition, this association might be observed between seizure disorders and risk of stroke because evidence suggests a link between bipolar disorder and epilepsy.[3] With these considerations, we examined the association between these two types of comorbidities and risk of stroke in our patients with bipolar disorder; however, results were not significant. The crude risk ratios of anxiety disorder and seizure disorders for the risk of stroke were 1.21 (95% CI 0.74–1.96, $P = 0.446$) and 2.18 (95% CI 0.35–13.49, $P = 0.403$), respectively, based on the case–crossover study.[1] These findings suggested that the association between acute exposure to mood stabilisers and risk of stroke in patients with bipolar disorder may not be confounded by anxiety and seizure comorbidities.

We agree with the comment that the role of psychosocial factors in stroke should be addressed in patients with bipolar disorder. Information on these variables was unavailable in the National Health Insurance Research Database (NHIRD) of Taiwan; this is one of the limitations of this study. However, the design of a case–crossover study has the advantage that study participants serve as their own controls and therefore this may minimise the effects of such unmeasured variables.

We would also like to address the limitation issues indicated by Kuppili and colleagues. In Taiwan, the prescription of oral contraceptive pills is not covered by national health insurance. Therefore, the effect of oral contraceptives on the association between valproic acid use and risk of stroke cannot be excluded.

https://doi.org/10.1192/bjp.2019.64 Published online by Cambridge University Press

In addition, medication adherence is not available in the NHIRD. Therefore, these points should be considered as limitations of our study.

Finally, we defined the use of carbamazepine, valproic acid, lithium or lamotrigine as the use of any mood stabiliser. Guidelines have suggested that combination therapy is an acceptable strategies for treating bipolar disorder.[4] Similar to the results of our prior study,[5] we believe that combination therapy for bipolar disorder may have contributed to the gap between the number of patients receiving any mood stabiliser and the sum of patients as per the numbers given separately for carbamazepine, valproic acid, lithium and lamotrigine in our study.

References

1 Chen PH, Tsai SY, Pan CH, Chang CK, Su SS, Chen CC, et al. Mood stabilisers and risk of stroke in bipolar disorder. *Br J Psychiatry* 2019; **214**: 305.

2 Pavlova B, Perlis RH, Mantere O, Sellgren CM, Isometsä E, Mitchell PB, et al. Prevalence of current anxiety disorders in people with bipolar disorder during euthymia: a meta-analysis. *Psychol Med* 2017; **47**: 1107–15.

3 Wotton CJ, Goldacre MJ. Record-linkage studies of the coexistence of epilepsy and bipolar disorder. *Soc Psychiatry Psychiatr Epidemiol* 2014; **49**: 1483–8.

4 Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord* 2013; **15**: 1–44.

5 Yang SY, Liao YT, Liu HC, Chen WJ, Chen CC, Kuo CJ. Antipsychotic drugs, mood stabilizers, and risk of pneumonia in bipolar disorder: a nationwide case-control study. *J Clin Psychiatry* 2013; **74**: e79–86.

Chian-Jue Kuo, Attending Psychiatrist, Taipei City Psychiatric Center, Taipei City Hospital; and Associate Professor, Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taiwan; **Pao-Huan Chen**, Lecturer, Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University; and Attending Psychiatrist, Department of Psychiatry and Psychiatric Research Center, Taipei Medical University Hospital, Taiwan. Email: tcpckuo@seed.net.tw

doi:10.1192/bjp.2019.64

Timing of onset of lithium relapse prevention - how early, how late?

In a recent paper, Dr Taylor raises an important issue: how long does it take for people with bipolar disorder to respond to lithium treatment?[1] In meta-analysis of data from three clinical trials, he found that patients randomised to lithium had significantly lower relapse rates than those receiving placebo, even in the first 2 weeks of treatment. This conclusion, however, does not answer the more relevant question as to how long a treatment trial should last before it can be established whether it is effective. In other words, is it worth waiting for let us say a year before switching to another option?

Clinical experience would suggest that there is a great range of time to response, which may relate to diagnostic and genetic heterogeneity.[2] Some patients respond within a few weeks whereas others may continue having major mood symptoms during the first year of treatment. Patients in the latter group will be inevitably categorised as 'non-responders' if even a single relapse is the criterion of treatment failure.

In Dr Taylor's study all three trials were based on discontinuation designs and were enriched for acute response to quetiapine or lamotrigine. However, enriched discontinuation designs with time to relapse as the outcome variable are less than ideal for evaluation of treatments of an illness that runs a lifelong course that is often highly unpredictable. Furthermore, most recent studies of long-term treatment of bipolar disorder (including the three trials discussed here) evaluate continuation treatment rather than recurrence prevention.

With respect to the minimal necessary length of treatment trial, there is practically no systematic data and the existing bipolar treatment guidelines stay away from the subject as well. In an earlier study, Ahrens *et al* attempted to estimate the time needed for patients to benefit from the suicide-reducing effect of lithium; they concluded that a treatment period of at least 2 years was necessary to return suicide risk to population baseline.[3] Given this, a more realistic design of maintenance studies might consider different outcome criteria such as affective morbidity assessed periodically over a sufficiently long observation period. As for a practical decision as to how long a treatment trial needs to last, it may become easier with advances in personalised treatment and discoveries about predictors of treatment response. Then it should be possible to individualise the length of a treatment trial – longer in those people expected to benefit from a specific treatment and abandon unsuccessful treatment earlier in those where the likelihood of response is equivocal.

References

1 Taylor MJ. Timing of onset of lithium relapse prevention in bipolar disorder: evidence from randomised trials. *Br J Psychiatry* 2018; **213**: 664–6.

2 Manchia M, Cullis J, Turecki G, Rouleau GA, Uher R, Alda M. The impact of phenotypic and genetic heterogeneity on results of genome wide association studies of complex diseases. *PLoS One* 2013; **8**: e76295.

3 Ahrens B, Muller-Oerlinghausen B, Grof P. Length of lithium treatment needed to eliminate the high mortality of affective disorders. *Br J Psychiatry* 1993; **163** (suppl 21): 27–9.

Nathan Corbett, MD. Resident, Department of Psychiatry, University of Toronto, Canada; **Martin Alda**, MD FRCPC. Professor and Killam Chair in Mood Disorders, Department of Psychiatry, Dalhousie University, Halifax, Canada. Email: malda@dal.ca

doi:10.1192/bjp.2019.65

Author's reply

Corbett & Alda raise the interesting question of how long a treatment trial should last before it can be established whether lithium is effective for a specific individual. As they note, existing experimental studies are not necessarily designed to address that particular question, which raises significant conceptual and analytic challenges.

Their interesting suggestion of assessing maintenance treatments through comparison of cumulative morbidity over long periods may be becoming a more feasible prospect through the combination of electronic health records analysis[1] with the increased availability of longitudinal mood monitoring outside experimental studies.[2]

Pending these new data, the available evidence indicates that lithium is likely to reduce the risk of manic relapse rapidly, whereas full effects against depressive relapse probably develop over a longer period.[3]

References

1 Hayes JF, Pitman A, Marston L, Walters K, Geddes J, King M, et al. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: a UK population-based electronic health records study. *JAMA Psychiatry* 2016; **73**: 630–7.

2 McKnight RF, Bilderbeck AC, Miklowitz DJ, Hinds C, Goodwin GM, Geddes JR. Longitudinal mood monitoring in bipolar disorder: course of illness as revealed through a short messaging service. *J Affect Disord* 2017; **223**: 139–45.

https://doi.org/10.1192/bjp.2019.64 Published online by Cambridge University Press