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doi: 10.1192/bjp.205.5.409a

BDNF and proBDNF as biomarkers for bipolar disorder

I read with great interest the recent article by Li *et al*, describing plasma levels of brain-derived neurotrophic factor (BDNF) in patients with bipolar disorder in their first depressive episode.[1] A total of 203 patients with a first major depressive episode, as well as 167 healthy controls, were enrolled. After 3 years of bi-annual follow-up, 164 patients with a major depressive episode completed, and of these, 21 patients were diagnosed as having bipolar disorder and 143 patients were diagnosed as having major depressive disorder. At baseline, patients with bipolar disorder and depression showed significantly lower BDNF mRNA levels ($P<0.001$ and $P=0.02$, respectively) and plasma BDNF levels ($P=0.002$ and $P=0.01$, respectively) compared with healthy controls. Interestingly, plasma BDNF levels in patients with bipolar disorder were lower than those in patients with depression.

This study suggests that the model for predicting bipolar disorder during a first depressive episode is a combination of BDNF mRNA with plasma BDNF levels.[1] BDNF (mature BDNF) is a 13 kDa polypeptide, which is initially synthesised as a precursor protein, preproBDNF, in the endoplasmic reticulum. Following cleavage of the signal peptide, proBDNF (~32 kDa) is converted to mature BDNF by extracellular proteases. It was initially thought that only secreted, mature BDNF was biologically active, and that proBDNF, localised intracellularly, served as an inactive precursor. However, accumulating evidence shows that both proBDNF and mature BDNF are active, eliciting opposing effects via the p75NTR and TrkB receptors, respectively, and that both forms play important roles in several physiological functions.[2]

The enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems) used by Li *et al* recognise both proBDNF (precursor of BDNF) and mature BDNF, because of the limited specificity of the BDNF antibody.[3] Using newly available human proBDNF and mature BDNF ELISA kits, which differentiate between the BDNF forms, we have reported high levels of both proBDNF and mature BDNF in human serum.[3] We reported that serum levels of mature BDNF, but not proBDNF, in patients with major depressive disorder were significantly lower than those in healthy controls.[4] And we recently found that serum levels of mature BDNF and the ratio of mature BDNF to proBDNF in mood-stabilised patients with bipolar disorder were significantly higher than in healthy controls.[4] Interestingly, serum levels of proBDNF in mood-stabilised patients with bipolar disorder were significantly lower than those in healthy controls.[5] These findings were confirmed in two independent cohorts (Sahlgrenska set and Karolinska set in Sweden).[5] Considering the high levels of both proBDNF and mature BDNF in human serum, and their putative opposing functions, it would be clinically and scientifically interesting to measure the individual serum levels of proBDNF and mature BDNF in this cohort study.

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doi: 10.1192/bjp.205.5.410

Declaration of interest

K.H. is a holder of the patents 'Diagnostic and examination method for eating disorder' (US 7,754,434 B2) and 'Diagnostic agent for ischemic heart disease risk group' (US 2013/0310321A1), which pertain to the measurement of BDNF as a biomarker. In addition, He has served as a scientific consultant to Astellas and Taisho and he has received research support from Abbvie, Dainippon Sumitomo, Otsuka and Taisho.

Authors' reply: While we agree with Professor Hashimoto's comments regarding the predictive role of mature brain-derived neurotrophic factor (mBDNF) and its precursor, proBDNF, in bipolar disorder, several points merit further discussion.

First, we presented preliminary data describing a potential role for BDNF as a biomarker for predicting bipolar disorder in major depressive disorder, although we detected the serum BDNF level using commercial kits that do not differentiate between mBDNF and proBDNF. When we reviewed the literature regarding mBDNF and proBDNF in bipolar disorder and major depressive disorder, we noticed that lower serum levels of mBDNF and higher serum levels of proBDNF were found among patients with major depressive disorder.[1,2] Södersten *et al* also reported that higher serum levels of mBDNF and lower proBDNF were observed among patients with bipolar disorder.[3] These disparate results suggest that levels of mBDNF and proBDNF, as well as the ratio of mBDNF to proBDNF, might be sensitive enough to help differentiate bipolar disorder from major depressive disorder.

Second, our previous studies indicated that BDNF probably has some sex-specific characteristics. Tang *et al*[4] reported that the ratio of mBDNF to proBDNF differs in a sex-specific manner in zebra finches. These findings suggest that mBDNF and proBDNF are different in males and females and should be further investigated.

Third, the findings of one of our previous studies implied that genetic interactions between genes encoding BDNF and its receptor enhance the risk of treatment-resistant depression.[5] Recent studies have found that mBDNF and proBDNF elicit biological effects via interaction with their respective receptors, p75NTR and TrkB. Accordingly, we concluded that evaluations of mBDNF and proBDNF should also consider their receptors. On the whole, we appreciate Professor Hashimoto's insightful comments in directing our future work.

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https://doi.org/10.1192/bjp.205.5.410a Published online by Cambridge University Press

and its precursor proBDNF in mood-stabilized patients with bipolar disorder: A study of two independent cohorts. *J Affect Disorders* 2014; **160**: 1–9.

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doi: 10.1192/bjp.205.5.410a

Early and delayed treatment of bipolar disorder

Using Danish registry data, Kessing *et al* examined the relationship between lithium response and the timing of treatment (early *v.* delayed).[1] Early treatment was associated with an increased probability of lithium response. This is a clinically important finding, given the increasing emphasis on early intervention in bipolar disorder. The results of the Kessing *et al* study are sobering. Only few patients, particularly among those for whom treatment was delayed, responded to lithium. Several factors may have contributed to the reported results.

The study did not – and possibly could not – control for the cycle shortening that is observed after successive episodes of bipolar disorder. Although the interpretation of such cycle shortening has been debated,[2] it is well established that early cycles are significantly longer than those occurring later; consequently, early in the course of illness one would expect longer spontaneous remissions regardless of treatment. This effect may be partially responsible for the greater treatment response in patients receiving early intervention in the Kessing *et al* study.

Naturalistic studies typically demonstrate full response in about 30% of participants[3] (that is, no recurrences, or the Kessing *et al* criterion, in treatment-adherent patients), which is markedly greater than the response rate observed by Kessing *et al*. This discrepancy could be related to age at first contact. The average age of participants whom Kessing *et al* reported as having received early and late treatment was 46.7 years and 49.1 years, respectively. The natural history of bipolar disorder includes an average age at onset in the second or third decade of life. The trajectory of the illness, where mania typically develops as the last stage, delays the diagnosis of bipolar disorder. Also, there is often a substantial delay in starting treatment even following the diagnosis of bipolar disorder.[4,5] These reports, in conjunction with the advanced age at index presentation, and high rates of antidepressant, antipsychotic and anticonvulsant use in the Kessing *et al* study suggest that participants may have been afflicted with bipolar disorder for some time before 'first contact'. In a sample of 450 participants, Baldessarini *et al* reported a negative relationship between treatment latency and effect of treatment on time spent ill.[5] If the aforementioned findings are generalisable to the Danish sample, the reduced overall treatment responses may be interpreted as a consequence of relatively advanced participant age.

Finally, Kessing *et al* analysed data collected since 1995. Is it possible that participants had received lithium during the years prior? This would further complicate the interpretations of sample responsiveness to lithium, regardless of early or late initiation. In conclusion, we suggest that the findings presented by Kessing *et al* are limited by the lack of control for inter-participant differences in the manifestation of the natural history of bipolar disorder. Such control may be difficult, or in some cases impossible, to achieve using registry-based observational data, but is nevertheless imperative to understanding the effects of early *v.* late treatment prophylaxis in relapsing–remitting illnesses such as bipolar disorder.

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doi: 10.1192/bjp.205.5.411

Authors' reply: We are confident that the relatively low response rates to lithium in our study relate to the narrow definition of lithium response, rather than to characteristics of the included patients.[1] Thus, we intended to characterise patients who had an excellent response to lithium monotherapy; that is, patients who were 'cured' from further affective episodes following a start-up period of lithium as in a prior study.[2] We used two robust clinical indicators to define excellent lithium response: (a) lithium prescribed in monotherapy; and (b) no need for psychiatric hospital admission. By doing this, we defined lithium response in a rather rigorous way, resulting in relatively low rates of response. We do not find that our definition of lithium response hampered the finding of the study that early treatment with lithium was associated with increased probability of excellent lithium response compared with delayed treatment, or hampered the generalisability of this finding. Although cycle acceleration occurs on average in bipolar disorder[3,4] the results of our study may suggest that early treatment with lithium might prevent progression of bipolar disorder.

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doi: 10.1192/bjp.205.5.411a

'Reasonable adjustments' for vulnerable patients

We support the views of Tuffrey-Wijne & Hollins[1] and their argument for the NHS to take an organisational approach to embed documentation and provision of reasonable adjustments for those with protected characteristics under the Equalities Act 2010. Lord Darzi defined quality for the NHS as comprising three dimensions: safety, effectiveness and patient experience.[2] The provision of reasonable adjustments is central to each of these.

Safety – Tuffrey Wijne & Hollins rightly identify the lack of provision of reasonable adjustments as being a patient safety issue. The Confidential Inquiry into Premature Deaths of People with

https://doi.org/10.1192/bjp.205.5.410a Published online by Cambridge University Press