

Correspondence

Edited by Kiriakos Xenitidis and
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Contents

- Can we predict switch from unipolar depression to bipolar disorder?

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Li *et al* investigated the levels of brain-derived neurotrophic factor (BDNF) in patients with a first major depressive episode to assess the impact of these levels on the development of bipolar disorder during 3-year follow-up.¹ They found that a combination of the levels of BDNF messenger RNA (mRNA) and plasma BDNF predicted a switch from depression to bipolar disorder in the following 3 years, with an area under the receiver operating characteristics (ROC) curve of 0.80. Li *et al* claimed that BDNF levels serve as a differential diagnostic biomarker for bipolar disorder in patients with a first depressive episode. If physicians could predict future development of bipolar disorder during a first depressive episode using biomarkers, it would allow us to select optimum treatment strategies. However, some caveats should be noted in Li *et al*'s study.

First, in the sample studied by Li *et al*, the diagnostic conversion rate from depression to bipolar disorder during the 3-year follow-up was as high as 12.8% (i.e. a shift to bipolar disorder occurred in 4.3% of the patients per year). This rate is amazingly high compared with rates in previous studies: for example, 1.5% per year² and 2.3% per year.³ If the patients who dropped out were all assumed to remain unipolar depressed, the rate would be still high (10.3% in 3 years). The high conversion rate in this sample might be attributable to an inclusion of patients with previous (hypo)manic episodes that had been overlooked,⁴ and/or a liberal threshold for the diagnosis of a hypomanic or manic episode in the study. Caution should be exercised when generalising the findings of this study.

Second, the positive predictive value (PPV) of the combination of the levels of BDNF mRNA and plasma BDNF in detecting the future development of bipolar disorder was low, even if the high diagnostic conversion rate (12.8% in 3 years) was used; according to the ROC curve in Fig. 3,¹ the PPV was 48%, with sensitivity of 71% and specificity of 80%. This suggests that, of every two patients predicted to develop bipolar disorder within 3 years, using this biological index, one may be mislabelled as having latent bipolar disorder despite remaining unipolar depressed. Provided the diagnostic switch is assumed to occur in 6% of patients with a first depressive episode over 3 years after the onset of depression, as expected from previous studies,^{2,3} the PPV in this case would fall further, to 26%. Feasibility and clinical applicability cannot be undervalued.

We agree with the authors that BDNF can be linked with the pathophysiology of mood disorders, and that the impact may be more evident in bipolar disorder. However, before considering BDNF as a differential diagnostic biomarker in clinical settings, the low conversion rate from depression to bipolar disorder and the resulting low PPV ought to be taken into account.

1 Li Z, Zhang C, Fan J, Yuan C, Huang J, Chen J, et al. Brain-derived neurotrophic factor levels and bipolar disorder in patients in their first depressive episode: 3-year prospective longitudinal study. *Br J Psychiatry* 2014; **205**: 29–35.

- 2 Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord* 2005; **84**: 149–57.
- 3 Holma KM, Melartin TK, Holma IA, Isometsa ET. Predictors for switch from unipolar major depressive disorder to bipolar disorder type I or II: a 5-year prospective study. *J Clin Psychiatry* 2008; **69**: 1267–75.
- 4 Bschor T, Angst J, Azorin JM, Bowden CL, Perugi G, Vieta E, et al. Are bipolar disorders underdiagnosed in patients with depressive episodes? Results of the multicenter BRIDGE screening study in Germany. *J Affect Disord* 2012; **142**: 45–52.

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doi: 10.1192/bjp.206.1.79

Authors' reply: Recent studies have demonstrated that the rate of switching from unipolar depression to bipolar disorder has been underestimated. Frankle *et al* showed that, over a period of nearly 3 years, out of 160 patients with a major depressive disorder episode, 33 patients receiving antidepressants and 17 patients not receiving antidepressants switched to bipolar disorder.¹ The switch rate was 15.2% in patients who did and 17.6% in patients who did not take antidepressants. Holma *et al* performed a 5-year naturalistic study and found that 29/248 (11.7%) patients with previous unipolar depression switched to bipolar disorder.² Of these 29 patients, 22 patients switched to bipolar disorder II and 7 patients switched to bipolar disorder I.

Switching from depression to bipolar disorder can involve natural transition or antidepressant-induced transition. Wada *et al* reported that 7/33 (21.2%) patients developed bipolar disorder during 1 year of antidepressant treatment.³ Jin *et al* carried out a study of the rate of switching from depression to bipolar disorder in patients taking different classes of antidepressants.⁴ They demonstrated that the overall switch rate was 14.4% over 6 years. The switching rates for the different antidepressant types was as follows: 9.1% for selective serotonin reuptake inhibitors (SSRIs), 22.8% serotonin–noradrenaline reuptake inhibitors (SNRIs), 14.6% for noradrenergic and specific serotonergic antidepressants (NaSSAs), 27.2% for tricyclic antidepressants, and 36% for combination treatment with any two antidepressants. Thus, the rate of switching from unipolar depression to bipolar disorder has been demonstrated to be beyond even our expectation.

We agree with Sugihara & Tajika's comments regarding the prediction of switch from unipolar depression to bipolar disorder. It is in fact difficult to identify bipolar disorder when patients present with depression in their first episode. In our pilot study,⁵ neither plasma BDNF levels nor gene expression level of BDNF alone could differentiate major depressive disorder from bipolar disorder in the first depressive episode; the best model for predicting bipolar disorder in the first depressive episode was the combination of BDNF gene expression and plasma BDNF levels. It indicated that more relative biological biomarkers should be integrated to improve PPV. Furthermore, clinical characteristics are also important predictive factors for bipolar disorder.^{2,6} Predicting bipolar disorder becomes more accurate and reliable when we integrate more biological biomarkers and clinical characteristics of patients. Therefore, we are performing another study to construct a model to predict bipolar disorder in the first depressive episode that includes biological biomarkers and clinical characteristics.

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- 2 Holma KM, Melartin TK, Holma IA, Isometsä ET. Predictors for switch from unipolar major depressive disorder to bipolar disorder type I or II: a 5-year prospective study. *J Clin Psychiatry* 2008; **69**: 1267–75.
- 3 Wada K, Sasaki T, Jitsuiki H, Takaishi Y. One-year outcomes of unipolar depression patients with manic or hypomanic switch during acute antidepressant treatment. *Int J Psychiatry Clin Pract* 2013; **17**: 219–22.
- 4 Jin W, Ma Y, Qiu D, Wang G, Wang X, Fan X, et al. Comparison of switching rate from depression to BPD between different classes of antidepressants [Chinese]. *Chin J Nerv Ment Dis* 2007; **33**: 565–6.
- 5 Li Z, Zhang C, Fan J, Yuan C, Huang J, Chen J, et al. Brain-derived neurotrophic factor levels and bipolar disorder in patients in their first depressive episode: 3-year prospective longitudinal study. *Br J Psychiatry* 2014; **205**: 29–35.
- 6 Forty L, Smith D, Jones L, Jones I, Caesar S, Cooper C, et al. Clinical differences between bipolar and unipolar depression. *Br J Psychiatry* 2008; **192**: 388–9.

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doi: 10.1192/bjp.206.1.79a

Correction

Towards a more nuanced global mental health. *BJP*, 204, 415–417.
Reference 10 should read:

- 10 Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry* 2007; **68**: 654–61.

doi: 10.1192/bjp.206.1.80