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Disclosure

Both authors are scientific consultants for Medibio LTD. GP has served as consultant for Lundbeck and Pfizer.

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FK506 binding protein 5 (FKBP5) gene polymorphisms and their relationship with pharmacological response in bipolar disorders

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Scaini et al. offer an informative review of current knowledge about the neurobiology of bipolar disorders,[1] discussing the over-expression of FK506-binding protein 51 (FKBP51) as a putative mechanism conferring increased risk of mood dysregulation in bipolar disorders.

FKBP51 is involved in the hypothalamic pituitary axis feedback loop by acting as a co-chaperone for the sensitivity of the glucocorticoid receptor.[1] This mechanism is of importance because FKBP51 could decrease the glucocorticoid receptor's affinity for circulating glucocorticoids and help explain the dysfunctional negative feedback of the hypothalamic pituitary axis, which could be responsible for the increased vulnerability to mood episodes in bipolar disorders.[1,2]

FKBP51 is expressed by the FKBP5 gene, which is located on chromosome 6p21.[2,3] FKBP5 has been shown to be involved in the etiology of mood disorders, as well as in susceptibility to treatment response in mood disorders.[2] Certain FKBP5 allele variants have been associated with exaggerated expression of the FKBP5 gene, resulting in FKBP51 over-expression. Three high induction alleles of major FKBP5 gene polymorphisms are believed to enhance FKBP5 mRNA expression following glucocorticoid receptor activation, including rs1360780 (T-allele), rs3800373 (C-allele), and rs4713916 (A-allele).[3]

In order to confirm previous reports[3] of the role of FKBP5 high induction alleles, a systematic search of the literature on bipolar disorders, including PubMed, EMBASE, PsycINFO, Cochrane Library and Ovid MEDLINE, was conducted to identify studies that investigated FKBP5 polymorphisms in relation to treatment response in mood disorders. Studies were included if: 1) patients had mood disorders; 2) the disorders were diagnosed according to DSM or ICD classification systems; 3) the design was longitudinal; and 4) assessed response according to validated rating scales, expressed as odd ratios and 95% confidence intervals (95%CI). Eight studies met the criteria and included patients with unipolar and bipolar disorders, which allowed comparison between high and low induction alleles (detailed information available upon request via danilo.arnone@uaeu.ac.ae).

A random effects model meta-analysis was conducted in STATA to create a summary effect size and assess publication bias to investigate the relationship between high induction FKBP5 single nucleotide polymorphisms rs1360780, rs3800373, and rs4713916 and treatment response in mood disorders. The analysis of the rs4713916 FKBP5 A-high induction allele, obtained by combining three samples (two included patients with bipolar disorders),[4,5] indicated that carriers of this polymorphism are more likely to respond to treatment in mood disorders (effect size: 1.28; 95%CI 1.04-1.57). The analysis was free of heterogeneity (χ^2 = 1.01, degrees of freedom = 2, p = 0.6) and publication bias (Coef = 0.16, p = 0.3) (Figure 1). Analyses of the other two high induction alleles of FKBP5 polymorphisms showed no significant effect (rs1360780 effect size: 1.19; 95%CI 0.87-1.62; and rs3800373 effect size: 1.22; 95%CI 0.86-1.72) in the absence of publication bias (all p-values $>$ 0.05).

The results suggest that the high induction allele of rs4713916 in FKBP5 might increase susceptibility to treatment response in mood disorders. Further work is

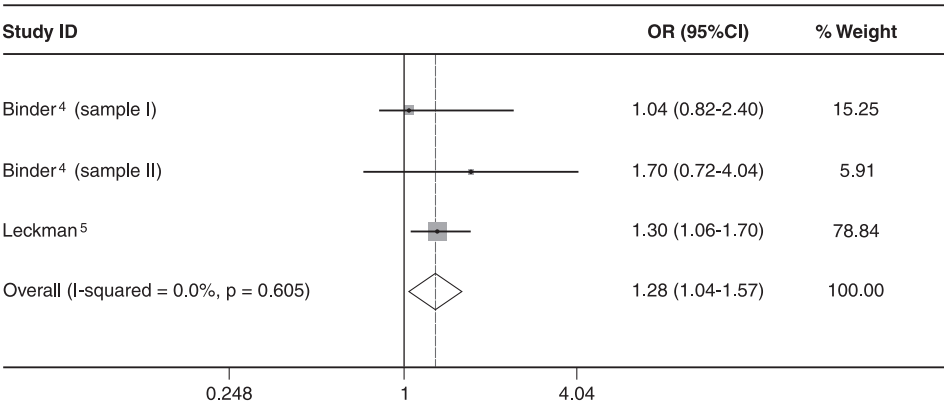

Figure 1 Meta-analysis of rs4713916 FKBP5 A-high induction allele.

required to more clearly determine the role of FKBP5 rs4713916 in bipolar disorders.

Danilo **Arnone**

Centre for Affective Disorders, Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. Department of Psychiatry and Behavioral Science, College of Medicine and Health Sciences, United Arab Emirates University (UAEU), Abu Dhabi, United Arab Emirates.

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Tokophobia Assessment Questionnaire: a new instrument

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Tokophobia is a pathological fear or avoidance of childbirth, which has received little attention and has been often neglected.[1] This condition negatively influences the pregnant woman's life or the acceptance of her pregnancy; it leads to the extension of pregnancy duration or motivates requests for caesarean sections. After birth, tokophobia may also delay bonding between the mother and the newborn, leading to breastfeeding difficulties and increasing the risk of puerperal depression.[2] Tokophobia is associated with intrauterine growth restriction, low birth weight, changes in fetal heartbeat, and prematurity, which are probably due to uterine artery dysfunction, a phenomenon that has been identified in pregnant women. However, the long-term effects on the child's development have not yet been established.[3]

Most surgeries are performed electively with no obstetric indication, using the phobia as an excuse. Due to the very peculiar characteristics of the judicialization of medicine, the convenience and financial accessibility of cesarean delivery, as well as the actual fear of childbirth, there has been a reduction in the incidence of vaginal birth, which has increased the cost of giving birth, as well as its complications.[4]