Response to letter from Dr Terao:

Olga Eyre, Vikram Patel, David Brent, Anita Thapar

We thank Terao for their response to our seminar on depression in young people[1]. Terao highlights that depression is often the first manifestation of bipolar disorder and early onset depression is a risk factor for switching to bipolar disorder. This is an important clinical point.

However, rates of manic switch in young people with Major Depressive Disorder (MDD) vary considerably across studies ranging from 8% to 48.6%[2-4]. Although a proportion who experience depression in childhood or adolescence will go on to develop bipolar disorder, it is worth noting that the conversion rate of 48.6% cited by Terao[5] is atypically high.

A number of factors have been found to predict switch from MDD to bipolar disorder in young people. In addition to earlier onset of depression, these include family history of mood disorders (including bipolar disorder and MDD), subthreshold mania, or depression accompanied by emotional dysregulation, behavioural problems or psychotic features[4]. There is also evidence to suggest higher rates of switch to bipolar disorder in young people with depression who also have ADHD[6]. Variation in sampling may explain the wide range of rates observed, including the high rate of conversion seen in the study cited by Terao[5]. The cited study was a small sample taking part in a medication trial. It included only individuals with prepubertal depression, who had high rates of family history of bipolar disorder. Therefore, findings are unlikely to be representative of most young people experiencing adolescent depression.

Another factor that may explain varying rates of switching across studies include the definition of bipolar disorder used (with higher rates of switch where Bipolar II is included), and the length of follow up (longer study follow up resulting in higher rates). It should be noted that there has been some controversy in recent years regarding the diagnosis of bipolar disorder in children and young people, particularly in the US, where it was suggested by some that mania in childhood can present as chronic, persistent irritability without elevated mood[7]. This resulted increased rates of paediatric bipolar disorder diagnosis in the 1990s to 2000s[8]. It is now clear that these children do not have paediatric bipolar disorder, but instead

are at increased risk for unipolar depression. However, none of the studies cited here used this definition.

The final important point made in Terao's response to our seminar, was the need to consider risk of antidepressant induced manic switch in young people with depression. Antidepressant use has been found to increase the rate of switch to mania, hypomania or mixed states in individuals with MDD, with the risk particularly high in young people, at around 9-10% [9,10]. This does emphasise the need to carefully monitor all young people who are prescribed antidepressant medication, in particular those with risk factors predisposing them to manic switch.

References:

1. Thapar A, Eyre O, Patel V, Brent D (2022). Depression in young people. *Lancet*; 400 (10352): 617-31.
2. Beesdo K, Höfler M, Leibenluft E, Lieb R, Bauer M, Pfennig A. (2009) Mood episodes and mood disorders: patterns of incidence and conversion in the first three decades of life. *Bipolar Disord*;11(6) :637-49.
3. Jonsson U, Bohman H, von Knorring L, Olsson G, Paaren A, von Knorring AL (2011) Mental health outcome of long-term and episodic adolescent depression: 15-year follow-up of a community sample. *J Affect Disord*;130(3):395-404.
4. Uchida M, Serra G, Zayas L, Kenworthy T, Hughes B, Koster A, Faraone SV, Biederman J. (2015). Can manic switches be predicted in pediatric major depression? A systematic literature review. *J Affect Disord*; 172: 300-6.
5. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. *Am J Psychiatry* 2001; 158: 125–7.
6. Chen MH, Chen YS, Hsu JW, Huang KL, Li CT, Lin WC, Chang WH, Chen TJ, Pan TL, Su TP, Bai YM. (2015) Comorbidity of ADHD and subsequent bipolar disorder among adolescents and young adults with major depression: a nationwide longitudinal study. *Bipolar Disord*;17(3): 315-22.
7. Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, Mennin D (1995). Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry*; 34(7): 867-76.

8. Leibenluft E (2011). Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry*,168(2):129-142.
9. Baldessarini RJ, Faedda GL, Offidani E, Vazquez GH, Marangoni C, Serra G, Tondo L (2013). Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: A review. *Journal of Affective Disorders*; 148, 129-35.
10. Offidani E, Fava GA, Tomba E, Baldessarini RJ (2013). Excessive mood elevation and behavioral activation with antidepressant treatment of juvenile depressive and anxiety disorders: a systematic review. *Psychother Psychosom*;82(3):132-41.