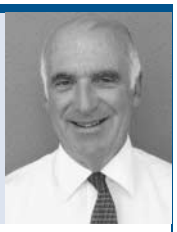
BJPsych | The British Journal of Psychiatry (2010) 196, 87–88. doi: 10.1192/bjp.bp.109.074898

Editorial

# Predicting onset of bipolar disorder from subsyndromal symptoms: a signal question?†



Gordon Parker

**Summary**
This issue reports a community-based study quantifying the extent to which subthreshold hypomanic or depressive symptoms in childhood or adolescence predicted subsequent formal bipolar disorder status and mental health service attendance. This editorial emphasises the low predictive power of the signal and considers early intervention implications.

**Declaration of interest**
G.P. serves on several advisory boards for psychotropic drugs, has chaired and spoken at meetings convened by pharmaceutical companies, and has received research and scientific meeting sponsorship by such companies.

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'Do not mistake a child for his symptom.'

Erik Erikson

In this issue, Tijssen and colleagues[1] report a study examining whether early expressions of subthreshold hypomanic or depressive symptoms from childhood through to early adulthood ('common bipolar experiences') are predictive of subsequent conversion to formal bipolar disorder and mental health service attendance. If a valid and distinctive signal, then there are obvious implications, particularly in advancing an argument for early intervention as an extension of the arguments we muster for improving formal detection. For example, many studies (see e.g. Hadjipavlou *et al*[2]) have quantified substantive subjective distress and disability, as well as considerable collateral damage (i.e. failure to maintain jobs and relationships, and increased risks of suicide, hospitalisation and drug and alcohol misuse) when the bipolar disorders remain undiagnosed and/or inadequately managed.

Although such arguments are persuasive for providing early intervention following formal onset of bipolar disorder, they may or may not hold for addressing indicative or prodromal symptom states. But does the study by Tijssen and colleagues make or advance such a case?

## Are early episodes indicative of later disorders and service use?

The researchers recruited a community-based adolescent sample with a mean age of 18 years at baseline assessment and, after excluding those with established bipolar disorder and mental health facility attendees at baseline or at early follow-up stages, they assessed outcome at a mean follow-up period of 8 years. Outcome variables were (i) onset of DSM-defined hypomanic or manic episodes (DSM (hypo)manic episodes) and (ii) mental healthcare attendance.

### Hypomanic or manic episodes

Those who had never experienced two or more hypomanic or manic symptoms before baseline assessment had a 0.7% risk of developing DSM (hypo)manic disorders at follow-up and a 9.4% risk of using mental healthcare services. As pre-baseline symptoms increased in number, the rate of DSM (hypo)manic episode conversion increased (but only to a maximum rate of 3.2%). Similarly, the more persistent such pre-baseline symptoms, the higher the DSM (hypo)manic episodes and mental healthcare services use transition rates.

### Depressive episodes

The authors also examined the impact of pre-baseline depressive symptoms and again showed a 'dose' impact: the greater the number and persistence of depressive symptoms, the higher the subsequent DSM (hypo)manic episodes and mental healthcare services use rates but, as might be anticipated, depressive symptoms had less impact and less of a 'dose' effect than pre-baseline hypomanic or manic symptoms.

## Early manic symptoms in adolescents – what may they signify?

The first refutability question is whether the predictor and outcome variables were confounded by artefactual issues. In essence, might those who 'converted' to full clinical diagnosis at follow-up have already had their bipolar disorder at baseline assessment, with some assessment nuance (e.g. person biases such as denial, rater biases emerging from interviewers only rating symptoms 'noticed by others' or causing 'problems', limitations to the screening measure, imperfect test–retest reliability to 'caseness' estimates of mood disorders) accounting for (false) subclinical classification at an early stage and (correct) clinical status at follow-up. The study's finding of dose effects (with more pre-baseline symptoms and greater symptom persistence increasing the 'conversion' rates) does not entirely negate that caveat, as milder and briefer pre-baseline symptomatology would risk false negative assignment at that time.

Second, although we recognise that bipolar disorder can commence in adolescence and in pre-pubertal children – with studies indicating that initial bipolar symptoms commence in one-half to two-thirds of individuals prior to the age of 19 years[3] – the impact of age on phenotypic expression in younger individuals is unclear, both in terms of pattern and severity. Most reviews (e.g. Youngstrom[4]) indicate age-based differences (e.g. irritability, hyperactivity and 'mixed states' being over-represented in younger individuals) as well as some similarities. Hence, were

†See pp. 102–108, this issue.



https://doi.org/10.1192/bjp.bp.109.074898 Published online by Cambridge University Press

the subclinical symptoms in study participants truly subclinical or, alternately, did they more reflect age-specific phenotypic manifestations of true bipolar status at a younger age – in essence, heterotypy?

Thus, did the presence of 'common adolescent bipolar experiences' reflect an incipient state as implied by Tijssen and colleagues – or more reflect the early expression of actual bipolar disorder? Until we know how to accurately stage and define the bipolar disorders (particularly in adolescents), we may assume that, in those who develop bipolar disorder later, some will show no early warning signs, some will meet full criteria in adolescence and earlier, some will show non-specific symptoms, some will show forme fruste symptoms and states (e.g. anxiety and eating disorders), and some will show subclinical or subthreshold symptoms – with only the last reflecting the logic of Tijssen *et al*'s study. If the reality is that quite variegated longitudinal patterns occur, any signal from subsyndromal symptoms will be compromised by the other patterns.

## Is early intervention in adolescents justifiable?

Tijssen and colleagues concluded that their findings may indicate 'a window for intervention', and referenced several studies indicating that early onset predicts a worse outcome for bipolar disorder. Can that next step be argued by their paper or is such a conclusion premature?

The latter is suggested – both by the theoretical issues noted above and by the quantitative analyses. First, for study participants who showed the greatest number of pre-baseline hypomanic subthreshold symptoms and the highest rate of symptom persistence, rates of conversion to a full bipolar diagnosis were 3.2% at most (in comparison to a conversion rate of less than 1% for those not reporting symptoms or 2.0% for those having brief symptoms). Essentially, the signal had low predictive power. As an analogy – although mental health professionals prioritise averting suicide, our capacity to predict the very small percentage of suicidally depressed individuals who go on to kill themselves is well recognised. If hospital admission protected against suicide, we would have to admit 100 such depressed individuals (for some quite variable period) to prevent the suicide of two or three. Such an analogy is relevant here when we compare the very low rates of conversion in comparison groups. The signal quantified in this study is weak and, when the much higher mental healthcare services use than DSM (hypo)manic episodes follow-up rates are considered, insufficiently specific to argue a case for intervention.

## A risky path

Some general concerns about intervening for preclinical states can be briefly overviewed. Many clinicians have great difficulty in making a bipolar disorder diagnosis even in those with established conditions (particularly the non-psychotic bipolar II disorders). Apart from failing to detect a bipolar pattern, many clinicians will interpret such patterns as reflecting normal mood swings, attention-deficit hyperactivity disorder, emotional dysregulation or a personality disorder. Other clinicians hold to a spectrum model for the bipolar disorders and risk including many with unipolar disorders as well as those who merely have colourful or ebullient personalities. Such risks of underdiagnosis and overdiagnosis are likely to be increased when assessing prodromal symptoms (by the nature of their low severity or non-specificity) – particularly in children and adolescents, as a consequence of their argot, response biases (e.g. denial), lack of worldly experiences and lifestyles. Let us consider the last only. DSM–IV hypomania criteria include inflated self-esteem, decreased need for sleep, pressured talk, distractibility and excessive involvement in pleasurable activities. Many adolescents would meet such individual DSM criteria as a consequence of a wide range of activities – including falling in love, extensive socialisation or studying for exams – all risking false positive diagnoses. The reported rise of 4000% in the diagnosis of bipolar disorder over the past decade in those under 18 years of age in the USA[5] may reflect better detection up to a point, but we must also be suspicious of overdiagnosis.

Low predictability and false positive interpretation of adolescent 'symptoms' would risk interventions (drug and non-drug) being provided to many who would never have developed the disorder. Further, if a drug intervention is to be offered, how to proceed when the evidence base across the differing drug classes for managing adolescent bipolar disorder is negligible?

A further risk to providing early intervention is the impact of labelling and stigma. The distinguished psychiatrist Norman Sartorius recounted a salutary personal story in his book dealing with mental illness stigma.[6] At the age of 8 he experienced distinct visual and auditory hallucinations. He received no treatment and the hallucinations went away, but he contemplates the impact on his subsequent schooling, socialisation and working life if, alternatively, he had been admitted to hospital or treated.

While Tijssen *et al* raise (in the Discussion) an argument for intervention, their summary has a differing emphasis – noting there that the 'non-clinical bipolar phenotype' is 'common and usually transitory'. In the early phases of the study, 28% of the sample experienced hypomanic or manic symptoms, while 60% experienced depressive symptoms. Yet only 1.1% met formal criteria for bipolar disorder at follow-up. Their data weight that interpretation – one or two bipolar symptoms in adolescence do not a case make, either for indicating the probability of incipient formal bipolar disorder or for intervention. The researchers have illuminated a key issue, but the signal requires much greater definition.

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First received 3 Dec 2009, accepted 16 Dec 2009

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https://doi.org/10.1192/bjp.bp.109.074898 Published online by Cambridge University Press