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Bipolar At-Risk Criteria: An Examination of Which Clinical Features Have Optimal Utility for Identifying Youth at Risk of Early Transition From Depression to Bipolar Disorders

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Background: **A clinical and research challenge is to identify which depressed youth are at risk of "early transition to bipolar disorders (ET-BD)." This 2-part study (1) examines the clinical utility of previously reported BD at-risk (BAR) criteria in differentiating ET-BD cases from unipolar depression (UP) controls; and (2) estimates the Number Needed to Screen (NNS) for research and general psychiatry settings.** ***Methods:*** **Fifty cases with reliably ascertained, ET-BD I and II cases were matched for gender and birth year with 50 UP controls who did not develop BD over 2 years. We estimated the clinical utility for finding true cases and screening out non-cases for selected risk factors and their NNS. Using a convenience sample (N = 80), we estimated the NNS when adjustments were made to account for data missing from clinical case notes.** ***Results:*** **Sub-threshold mania, cyclothymia, family history of BD, atypical depression symptoms and probable antidepressant-emergent elation, occurred significantly more frequently in ET-BD youth. Each of these "BAR-Depression" criteria demonstrated clinical utility for screening out non-cases. Only cyclothymia demonstrated good utility for case finding in research settings; sub-threshold mania showed moderate utility. In the convenience sample, the NNS for each criterion ranged from ~4 to 7.** ***Conclusions:*** **Cyclothymia showed the optimum profile for case finding, screening and NNS in research settings. However, its presence or absence was only reported in 50% of case notes. Future studies of ET-BD instruments should distinguish which criteria have clinical utility for case finding vs screening.**

Key words: screening/case finding/youth/bipolar disorder/ultra-high risk/at-risk criteria/validity/clinical utility index/number needed to screen

Introduction

Globally, the peak age at onset (AAO) of severe mental disorders such as bipolar disorders (BD) and psychotic disorders is late adolescence and early adulthood.[1–3] Since the turn of the century, researchers have begun to identify subgroups of help-seeking youth who are at ultra-high risk (UHR) of early transition from a late prodromal stage to a first episode of psychosis (FEP). The risk of transition varies between about 15% and 35% over 12–24 months, but it can be predicted by UHR criteria, namely the presence of a combination of a limited set of state, trait, and familial characteristics.[4,5] Furthermore, these features can be incorporated into screening tools that can be applied in a range of settings. This enables the early identification of UHR individuals who can be monitored prospectively through a critical period of enhanced risk for the onset of FEP and offered clinical interventions if appropriate.[6]

In keeping with the UHR concept in psychotic disorders, several tools to identify young people at increased risk of BD have been applied in research settings, specialist clinics, and tertiary referral centers.[7–11] To date,

the only instrument with published data on predictive validity in the peak AAO group is the BD at-risk (BAR) assessment tool.[7] The BAR tool has good reliability (free-range kappa 0.83), and incorporates generic risk factors (eg, being in the peak AAO range for BD onset) alongside a set of specific criteria, namely: cyclothymia co-occurring with depression, sub-threshold mania, and depression co-occurring with genetic risk (ie, a family history of BD). A case note audit of 173 systematically assessed referrals to the ORYGEN early intervention services (in Melbourne, Australia) found that 1 in 7 youth aged 15–24 years met criteria for at least 1 BAR subgroup (BAR+). In BAR+ cases, the transition rate to (hypo) mania was about 23% over an observation period of about 250 days compared with 0.7% in the BAR− controls.[7] In a further prospective study undertaken by the same research group (35 BAR+ cases matched with 35 BAR− controls), early transition to bipolar disorders (ET-BD) (14%) occurred in BAR+ cases only.[12] A sub-analysis ($N = 52$) of this case-control study demonstrated that sub-threshold mania was the most significant predictor of ET-BD in those youth with common mental disorders, such as depression and anxiety.[13]

Identifying BAR or UHR-BD criteria is clinically important, but published studies on all the available instruments have been limited to the centers where the assessment tools originated. The generalizability of BAR criteria to other clinical settings and locations, and the clinical utility and discriminant validity of the proposed criteria warrants further examination in larger samples of ET-BD cases. Critically, it is important to determine whether the BAR criteria can distinguish which youth with early onset depression are at risk of ET-BD (ie, who show transition within about 2 y).[5,6] Also, information is needed on how the BAR assessment tool might perform in day-to-day clinical practice, where the quality of case note recordings may be sub-optimal, and ratings of the presence or absence of specific signs and symptoms may be less reliable than in specialist or research settings that employ systematic assessments. This 2-part study aims to address the following:

First, using a case-control methodology we examine the:

1. Discriminant validity of the BAR criteria in differentiating ET-BD youth from unipolar depression (UP) controls, who were matched for gender and year of birth
2. Clinical utility of the original BAR criteria and of 5 additional clinical features for finding BD cases and for screening out non-cases
3. Number Needed to Screen (NNS) using comprehensive, systematic assessments undertaken in research settings.

Second, using a convenience sample we estimate:

4. the NNS if screening of case notes is undertaken in routine clinical practice.

Methods

The supplementary appendix provides further detailed descriptions of the sampling, rationale for selection of risk factors, additional information on statistics and other basic data.

The methods for part I and part II of the study are briefly summarized below.

Part I: Case-Control Study

Sample. This sample comprised of 100 cases (50 ET-BD; 50 UP) who were identified from de-identified data from systematic, comprehensive, clinical assessments that had previously been entered into 8 databases designated appropriate for data sharing (in accordance with the recommendations of the Organisation for Economic Co-operation and Development[14]).

The 50 ET-BD cases were selected if they met the following criteria: (1) there was reliable evidence that the first episode of mania or hypomania that met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[15] diagnostic criteria occurred between 15–25 years (eg, using data from assessments using the Structured Clinical Interview for DSM-IV) and (2) that the first (hypo)manic episode occurred within 2 years of a major depressive episode. These ET-BD cases were frequency matched for gender and year of birth to individuals with a diagnosis of UP. The 50 UP controls also met the criteria of reliable evidence that they had experienced a major depressive episode that met DSM-IV criteria between the ages of 15–25 years. The key characteristics of the final sample are shown in table 1.

Table 1. Characteristics of Cases With ET-BD and Controls With UP Who Were Matched for Gender and Year of Birth

Clinical Characteristics[a]	ET-BD ($N = 50$)	UP ($N = 50$)
Number of females	31	31
Median age (IQ range) in years		
1st episode minor depression	13.3 (8–16)	13.5 (8–16)
1st episode major depression	17.0 (15–20)	18.0 (16–22)
1st episode hypomania or mania	20.3 (17–23)	
Median number of mood episodes (IQR)[b]	4 (2–6)	3 (2–5)
Number with a comorbid mental disorder or ASUD	7	8

Note: ET-BD, Early Transition to Bipolar Disorder; UP, unipolar depression; ASUD, Alcohol or Substance Use Disorder.
[a]Median and inter-quartile range (IQR) are reported as the age range of the sample is truncated, or the characteristic was not normally distributed.
[b]Assessment of number of episodes is truncated to age ≤ 25 y (see text for details).

Measures—Extended BAR Criteria. Bechdolf et al's[7] BAR criteria explore the presence or absence of 4 clinical characteristics prior to the onset of the first episode of (hypo)mania. These 4 variables are used to identify 3 at-risk subgroups ([1] sub-threshold mania (Box 1); [2] depression and cyclothymic features; [3] depression and genetic risk of BD [family history of BD]). These criteria were supplemented by assessment of the presence or absence of 5 other clinical features that may be risk factors for the onset of BD I or II (see supplementary appendix for details): probable antidepressant-emergent elation; psychotic symptoms during a mood episode; psychomotor retardation; atypical depression (anergia and/or hypersomnia); and family history of (1) multiple generations (≥2) affected by mood disorders, or (2) other mood or alcohol and substance misuse disorders (ASUD).

Statistical Analysis. As described in the supplementary appendix, we used several established approaches to examine the statistical significance and clinical utility of the selected risk factors in differentiating between cases with ET-BD and UP controls. We focus on:

Box 1: Examples of Key Criteria From the BAR Assessment Tool (From Bechdolf et al[7])

Definition of Sub-threshold Mania

For at least 2 consecutive days but less than 4 days: period of abnormally and persistently elevated, expansive or irritable mood and at least 2 criteria from the list:

1. inflated self-esteem or grandiosity,
2. decreased need for sleep (eg, feels rested after only 3-hour sleep),
3. more talkative than usual or pressure to keep talking,
4. flight of ideas or subjective experience that thought are racing,
5. distractibility,
6. increase goal directed activity (either socially, at work, or sexually) or psychomotor agitation.

Key Exclusion Criteria

1. Past history of a treated or untreated manic episode of 4 days duration or longer.
2. Past treatment with a mood stabilizer (eg, lithium or anti-convulsants) for >6 weeks.
3. Past treatment with an antipsychotic for 3 weeks (15 mg per wk of haloperidol or equivalent dose of another medication).
4. Evidence from medical records of an IQ below the normal range.
5. Organic brain disorder.

1. OR and 95% CI were calculated for each clinical characteristic.

A review of original studies and meta-analyses of youth with mood disorders indicated that most of the clinical features being tested occurred in at least 1 in 10 participants (except multi-generational family history, for which we could not identify a reliable prevalence rate). Thus, assuming an overall sample prevalence of at least 10% for each variable, we estimated that the size of the sample gave 90% power at a 5% level to detect an OR ≥ 1.98 in the matched case-control analyses.

2. Clinical Utility Index (CUI): Mitchell notes that when using a risk factor or symptom to find true cases or screen out non-cases, the real world clinical relevance of any item will be reduced if it arises infrequently.[16] As such, the CUI is increasingly recommended as an alternative to sensitivity or positive predictive values etc. (data shown in the supplementary appendix), as it reflects both the discriminatory ability of a factor or criteria and its overall occurrence in the population being examined.[17] The CUI+ (= Positive Predictive Value × Sensitivity) represents an estimate of the utility of a symptom or risk factor in case finding (the Rule In accuracy). The CUI− (= Negative Predictive Value × Specificity) reflects the utility for screening out non-cases (the Rule Out accuracy).

We calculated the CUI+ and CUI− for each feature selected and report the scores according to Mitchell's[17] grading of utility: poor (0–0.2), fair (0.21–0.39), moderate (0.4–0.59), good (0.6–0.79), or excellent (>0.8). If the CUI+ exceeds the CUI−, an item is regarded as better for case finding; if the CUI− exceeds the CUI+, the item is better for screening. We report the overall CUI for those factors where either the CUI+ or CUI− were graded as good.

3. NNS: similar to the Number Needed to Treat, the NNS represents the number of patients that need to be screened to yield 1 additional, correct identification of a case or non-case, *beyond* those who are misidentified.[18,19] The NNS were estimated for each BAR criterion with significant OR and 95% CIs (see supplementary appendix for the formula).

Part II: Convenience Sample Study

Sample. With ethical approval, a convenience sample of 80 cases of DSM-IV mood disorders (40 individuals with UP and 40 with BD) attending general psychiatry outpatient clinics was identified.[20]

Measures. The case notes were screened using an itemized checklist and the frequency with which key clinical information was recorded as present or as absent was noted (see supplementary appendix for details). Data on the prevalence of missing information was extracted.[20]

Statistical Analysis—NNS for Routine Clinical Practice. The NNS for each BAR criterion with a good CUI+ or CUI− (in the case-control study) was re-calculated to take into account the rates of missing information in the clinical case notes.

Results

As shown in table 1, the ET-BD cases and UP controls were more likely to be female (62%), with similar AAO for minor and major mood episodes. There were marginal group differences in number of prior mood episodes (BD>UP) or comorbidity rates (UP>BD).

As shown in table 2, the OR estimates demonstrate that the risk factors that best discriminated between ET-BD cases and UP controls were, in order of magnitude: sub-threshold mania (OR: 16.9; 95% CI: 4.7, 61.8), cyclothymia (OR: 14.2; 95% CI: 5.4, 37.2), atypical depression (OR: 11.5; 95% CI: 3.6, 36.7), family history of BD (OR: 7.6; 95% CI: 1.6, 35.9), and evidence of probable antidepressant-emergent elation (OR: 3.4; 95% CI: 1.2, 4.9).

The CUI scores showed that cyclothymia had a good CUI+ (0.62) and CUI− (0.62) grading for discriminating ET-BD cases from UP controls. Also, these gradings suggest that cyclothymia has clinical utility for both case finding and screening. Other items had better utility for screening. Sub-threshold mania had a moderate CUI+ (0.46) and a good CUI− (0.62) grading, while probable antidepressant-emergent elation demonstrated a fair CUI+ (0.22) but a good CUI− grading (0.66). Family history of BD had a relatively poor CUI+ grading (0.20), but a moderate CUI− grading (0.54).

Table 3 shows that the NNS estimates for the 5 selected BAR items. In systematically assessed cases the NNS ranged from 1.7 (for cyclothymia) through to 5.0 (for family history of BD). In the convenience sample, the predicted NNS ranged from 3.5 to 6.9. The NNS for family history showed the smallest difference between research and clinical settings (rising from 5.0 to 5.9), reflecting the fact that the presence or absence of this criterion was routinely recorded in clinical practice (84% of case notes).

Discussion

Increasing attention is being given to the identification of youth at risk of a first onset episode of BD.[21] Previous research on screening for BD suggested that self-rating instruments, eg, the Mood Disorders Questionnaire,[22] may help to identify pre-existing, unrecognized cases of BD in older adults. However, they cannot be recommended for use as a screening instrument in individuals at risk of early transition from depression to BD.[23–25] As such, the need to better identify ET-BD has led to the appearance of several new "BAR" instruments that differ in terms of time for completion, complexity and comprehensiveness.[7–11] We chose to examine Bechdolf et al's[7] BAR assessment tool, which has the benefit of brevity, established reliability, and emerging evidence of predictive validity. The present study builds on the research on the BAR instrument and its criteria in 4 important ways. First, we applied the criteria in a new clinical setting and used them for the first time outside of the location where the assessment tool was developed and tested. Second, we assessed a set of extended BAR criteria in a larger number of ET-BD cases than previously studied (the largest

Table 2. Prevalence and Performance of Each Putative Risk Factors for Bipolarity in Differentiating Between Cases With ET-BD and Controls With UP

	ET-BD (N = 50)	UP (N = 50)	OR (95% CI)	Clinical Rule in Accuracy (CUI+)	Clinical Rule Out Accuracy (CUI−)	Overall Clinical Utility[a]
Bipolar at-risk criteria[b]						
Cyclothymia	39	10	14.2 (5.4, 37.2)	Good	Good	Case finding and screening
Sub-threshold mania	26	3	16.9 (4.7, 61.8)	Moderate	Good	Screening
Family history of BD	12	2	7.6 (1.6, 35.9)	Poor	Good	Screening
Additional risk factors[c]						
Probable antidepressant-emergent elation	21	8	3.4 (1.2, 4.9)	Fair	Good	Screening
Atypical depression	25	4	11.5 (3.6, 36.7)	Fair	Good	Screening
Psychomotor retardation	6	2	2.6 (0.5, 13.6)	Poor	Moderate	—
Psychotic mood episode	6	1	6.7 (0.8, 57.7)	Poor	Moderate	—
Family history of other mood disorders and/or ASUD	22	14	2.0 (0.9, 4.64)	Fair	Moderate	—
Multi-generational family history of mood disorders	3	0	3.1 (0.3, 31.1)	Poor	Moderate	—

Note: CUI, Clinical Utility Index (see text for details and numerical estimate of grading).
[a]Overall clinical utility is only reported if the item received a good grading for either the CUI+ or CUI−.
[b]Criteria from Bechdolf et al.[7]
[c]Factors identified from research literature (see supplementary appendix for details).

Table 3. Estimated NNS for Selected Clinical Features of Early Transition From Depression to Bipolar Disorders for Individuals Assessed by Structured Systematic Clinical Interview Schedules and the Predicted NNS in Routine Clinical Settings

Clinical Features	Overall Clinical Utility	NNS With Systematic Assessment	Proportion of Case Notes With Missing Data[a]	Predicted NNS in Routine Clinical Practice
Cyclothymia	Case finding and screening	1.7	51%	3.5
Sub-threshold mania	Screening	2.2	68%	6.9
Probable antidepressant-emergent elation	Screening	2.8	39%	4.6
Atypical depression	Screening	4.5	27%	6.2
Family history of bipolar disorder	Screening	5.0	16%	5.9

Note: NNS, Number Needed to Screen.
[a]The percentage refers to the proportion of clinical case notes that failed to report either the presence or absence of the clinical feature.

subgroup reported was 35 BAR+ cases).[7,12,13] Third, we identified 2 additional features, antidepressant-emergent elation and atypical depression, that may enhance the utility of the BAR tool to identify ET-BD in cases of major depression aged 15–25 years. Fourth, we use easily interpretable parameters for describing the performance of each criterion, as the CUI and NNS are easier to understand and potentially more relevant to the planning of screening or case finding than other measures such as ORs, sensitivity, specificity, or positive and negative predictive value.[16–19]

This study found that the 3 original BAR items plus 2 additional variables (a set which we will refer to as BAR-Depression or BAR-D criteria) occurred significantly more often in ET-BD cases compared to UP controls, and that these trait, state and familial markers demonstrated moderate to good clinical utility for screening out non-cases. The NNS for each criterion was highly acceptable for research settings (about 2–5). Although the NNS for each criterion was slightly higher in routine clinical settings (range about 4–7) this finding seems to parallel the original case note audit by Bechdolf et al[7] that revealed that 1 in 7 youth met at least 1 BAR criterion. Overall, the BAR-D items show lower utility for case finding, and only cyclothymia and sub-threshold manic symptoms showed good or moderate capacity to differentiate ET-BD from UP. Although the current performance of sub-threshold mania was modest, it has previously been found to be a significant predictor of imminent transition to mania in a small scale study using BAR criteria in Australia[13] and a large scale study of offspring of bipolar parents in the United States.[26] A challenge for the future will be to develop a consensus on the definition of the term, which parallels issues faced in psychosis research (on BLIPS and APS).

The current study suggests that cyclothymia has the optimum profile for case finding, screening and NNS. However, the apparent clinical utility of cyclothmia must be counterbalanced by 2 observations. First, while this temperamental feature can be reliably defined and assessed in the research datasets (eg, using established personality assessment schedules), its presence or absence was not reported in half of the clinical case notes examined (in the convenience sample). Second, while systematic clinical assessments can usually discriminate between cyclothymia and sub-threshold manic symptoms (and other forms of affective instability), it is not clear whether these trait and state phenomena are dependably differentiated in routine clinical practice.[25,27] Third, these variables may co-occur at a rate that is greater than previously anticipated.[28] Taking all these issues into account, we suggest that an important implication of the current study is that clinicians may need help to develop their skills in detecting cyclothymia as well as encouragement to routinely record its presence or absence in youth with depression.

The findings on family history of BD are worthy of further discussion. Clinical and research evidence suggests that family history of BD is one of the most robust predictors of future onset BD[29,30]; and we found that clinicians recorded information about family history more than any other risk factor for BD. However, the present study confirms that the overall prevalence of a positive family history of BD in general psychiatry datasets is lower that reported in specialist clinics and research environments.[31] Furthermore, the recent National Institute of Healthcare and Clinical Excellence (NICE) guideline on BD suggests that the presence of family history of BD in cases of depression should not be used to identify potential risk of BD[32] as it predicts both recurrent UP as well as BD[33] and genetic loading for BD alone may not be sufficiently discriminatory.[33] Also, recent research suggests that other factors, eg, AAO of BD in a parent, may play a role in heritability and the likelihood of early onset in offspring.[34] Given these data, our finding that family history of BD in depressed youth is better for screening than for case finding seems to be a conservative, but realistic proposition.

Antidepressant emergent elation appeared to demonstrate sufficient clinical utility for use as a screening

item. However, as noted in the supplementary appendix, a significant problem arose in assessing the "probable" presence of elation that may be associated with antidepressant.[35] The definition we used could be applied with moderate confidence only to the data derived from systematic assessments, and it was clear from scrutiny of the general psychiatry case notes that clinicians apply idiosyncratic criteria or do not document how they have operationalized the term (and they often use the term antidepressant emergent elation inter-changeably with antidepressant-emergent mood instability). As such, we suggest caution in regard to considering "probable" antidepressant-emergent elation as a BAR criterion until there is greater consensus on how to define and assess it, including agreement about the maximum duration of the time delay between prescription of an antidepressant and the onset of these mood changes, and the level of severity and duration of mood and other symptoms required.[35]

Recommending the use of atypical depressive symptoms for screening is less problematic, as increases or decreases in sleep, appetite, activity and energy, are key criteria for the diagnosis of depressive episodes. Unsurprisingly, the presence or absence of these features was recorded in more than 70% of case notes. Indeed, it is unclear why these features are not employed in screening more often as many, but not all, studies indicate their potential importance in differentiating BD from UP.[36–38]

The study has several limitations, most notably that none of the datasets we accessed was derived from studies designed for the purposes of assessing risk of ET-BD in the peak AAO period (15–25 y) and, while assessments used reliable and valid tools, many were retrospective, with many potential problems including recall bias. The age range was selected because it represents the peak AAO for BD, but it can be argued that these boundaries were somewhat arbitrary. Also, the 24-month time frame for transition from depression to BD can be viewed in the same light. However, we would argue that it represents a pragmatic decision based on research evidence and clinical relevance. First, research on UHR criteria for psychosis and related evidence regarding time to transition suggests that 2 years is a critical time period[39] and that rates of transition then start to fall. Second, we suggest that it would be feasible and justifiable to monitor depressed youth at risk of ET-BD for this time period to offer the prospect of early interventions as appropriate.[40]

Instead of using a prospective cohort study approach, we chose a case-control methodology. The rationale for the sampling strategy was that we wanted to ascertain a large number of ET-BD cases to maximize the statistical power of the clinical utility and NNS analyses. However, a weakness of this approach is that there is a risk of recall bias in the cases and controls, and that it assumes a degree of homogeneity in the clinical populations recruited into the original datasets we accessed and that the prevalence rates for the BAR risk factors in the case-control sample reflect the true prevalence in other clinical and community settings. Although the base rates for each criterion were within the predicted ranges, they were slightly lower than anticipated for some features (eg, psychotic symptoms and psychomotor retardation). This reduced the power to detect significant OR and may mean we have prematurely excluded some variables from the NNS analyses. The use of a convenience sample can also be criticized as a potential source of biases, although we emphasize that the data were only used in the prediction of the NNS in routine clinical practice. This calculation, by definition, required access to clinically representative, general psychiatry case records. Lastly, we decided that the recruitment procedure for the case-control study, the sample size and the nature of the available data meant it was inappropriate to explore any additive effects for combinations of risk factors, or to undertake survival analyses of time to transition associated with each risk factor. However, it is important to note that the largest NNS is the rate limiting step for screening (so effects on speed of transition or additive effects) does not change the workload for screening or case finding. These important issues are being addressed in a larger-scale prospective cohort study.

In conclusion, this study is the first we know of that examines the clinical utility and discriminant validity of each factor included in Bechdolf et al's BAR criteria[7] and of other selected trait, state and familial markers of risk of ET-BD in depressed youth. Cyclothymia in individuals with depression showed the optimum clinical utility, as it is useful for both case finding and screening, and showed the lowest NNS. Unsurprisingly, sub-threshold mania also showed utility. Other clinical features (family history of BD, probable antidepressant emergent elation and atypical depression) had better utility for screening out non-cases than for case finding.

We suggest that future prospective studies of BAR tools should report the clinical utility for screening and case finding of each criterion they include, alongside their NNS. In this way it will be possible to compare these different key aspects across studies and also to determine if some tools are more applicable to selected populations (eg, specialist mood clinics, early intervention in psychosis services, etc.). For example, the BAR-D tool may be more useful for screening young people with major depression who are in the peak age range for risk of ET-BD than for other populations.

Lastly, we draw attention to the widely held view that youth mental health research would benefit from a trans-diagnostic approach. This is particularly relevant in determining the longer-term trajectories of severe mental disorders, many of which demonstrate at least 1 episode of depression during the earliest clinical stages.[4–6,12,35] As such, it is of considerable interest that there appears to be convergence in the type of criteria being employed in psychosis and BD to define risk syndromes (combinations of

limited sets of state, trait and familial characteristics).[4,5,7] State characteristics examined in the BAR criteria, such as brief, attenuated of sub-syndromal manic symptoms, clearly parallel the descriptor used in psychosis.[4] There are also similarities in the risk rates for transition to psychosis[4,5] and to BD.[7,12] This would seem to indicate that it may be possible to develop a combined tool that could not only further our understanding not only of who is at risk of ET-BD, but also identify if any characteristics are unique to a "mood disorder trajectory" and which may be shared with individuals who make a transition to psychosis. Clinically, this may help to plan generic as well as specific interventions and treatments.[40] It would also provide opportunities for research into underlying pathophysiological mechanisms associated with transition.[6,35,37]

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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