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Translating Research Findings into Clinical Decision-Making Thresholds for Young People at Risk of Bipolar Disorders

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Abstract

Background: Although several screening methods can reliably detect Bipolar at Risk (BAR) criteria, researchers employ different statistics to report transition to Bipolar Disorders (BD). This hinders cross-study comparisons and translation of findings to clinical practice. This study highlights the potential utility of estimating Likelihood Ratios (LRs) and quantitative decision-making thresholds.

Methods: Participants were individuals aged 16 to 25 who sought help for at least one clinically significant mood episode from secondary mental health services in Newcastle, England. Individuals who met one or more BAR criteria were followed up for one year. We used Likelihood Ratios (LRs) to quantify the change in the certainty (for early transition to BD) conferred by the presence or absence of different BAR criteria and identified those with the highest probability of BD onset.

Results: The sample comprised 110 individuals with a mean age of 19.3; 26 individuals (23.6%) demonstrated early transition to hypo/mania. Positive LRs ranged from 1.08 (i.e., a small additional increase in probability of early transition) up to 5.38. Employing a treatment threshold of a positive probability of transition >50% would lead to three groups of individuals being offered immediate treatment (those with subthreshold mania; cyclothymia, depression and family history of BD; or anergia with/without hypersomnia).

Conclusion: Proposals for developing early intervention services for youth at risk of developing BD will need to consider the economic cost versus clinical benefit. This short communication attempts to demonstrate the advantages of estimating LRs and probabilities of transition in moving BAR research forward and expanding its clinical relevance.

Keywords: Bipolar disorder; At-risk; Likelihood ratios; Probabilistic reasoning; Clinical decision-making thresholds

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Introduction

Globally, the peak age at onset of depressive, psychotic, and Bipolar Disorders (BD) is late adolescence and early adulthood. To enhance opportunities for early intervention, researchers developed Ultra-High Risk (UHR) criteria to identify which help-seeking youth were most likely to experience full-threshold First Episodes of Psychosis (FEP) [1]. Using this 'close-in' strategy as a template, similar Bipolar-at-Risk (BAR) criteria were devised to identify clinical phenotypes likely to be associated with future onset of full-threshold BD [2]. It is suggested that individuals who meet one of more BAR criteria may be offered prospective monitoring through a critical period of increased risk for a hypo/manic episode and/or clinical interventions aimed at delaying or preventing BD onset [3,4].

A range of checklists, self-rated, semi-structured and structured instruments are used to assess BAR criteria. The tools vary in content, quality, sensitivity, and specificity, but the criteria share several common elements, namely they postulate that BAR subgroups may be recognized by the presence of (i) subthreshold syndromes comprised of symptoms that are quantitatively rather

than qualitatively different from full-threshold episodes and/or (ii) a combination of a limited set of state, trait, and familial characteristics. Using these observations, investigators have undertaken independent cross-sectional case-control and cohort studies and findings have been synthesized in published reviews [4,6-10]. Although research indicates that several screening methods can reliably detect an array of BAR criteria, studies employed different statistics to analyze clinical outcomes and the rate of new onset cases of hypo/mania and time to transition from BAR to BD varied with clinical setting [11]. As such, knowledge about the validity of BAR criteria has improved, but it remains difficult to translate the research findings into recommendations for clinical practice. In other branches of medicine, there is greater acceptance of the utility of metrics such as likelihood ratios and probabilistic reasoning (Bayes theorem) for predicting diagnosis/prognosis and making clinical judgements about optimal treatment thresholds; also, these metrics can be used to estimate other summary statistics, such as the diagnostic odds ratio, which can be used to compare findings across studies and incorporated in meta-analyses [12].

This short communication aims to explore how data from a prospective cohort study of young people who met established BAR criteria can be analyzed to estimate individual probabilities for early transition to hypo/mania. We then demonstrate how comparing findings with pre-set 'decision-making' thresholds can assist in planning services that might offer enhanced monitoring (so-called 'watchful waiting') or targeted clinical interventions (e.g., selecting a risk threshold for offering pharmacotherapy). We emphasize that our primary aim is to offer an example of the potential utility of these approaches and recognize that other investigators may prefer other BAR criteria, variable pre-test odds and/or different thresholds.

Material and Methods

This study is one of several undertaken as part of an 'early identification of mood disorders' research program (described online at https://fundingawards.nihr.ac.uk; reference: PB-PG-0609-16166 and at https://www.cntw.nhs.uk/NTW/Research-984729) and received ethical approval from the regional committee (REC ref: 12/NE/0325). Below we summarize key aspects of the methodology relevant to this article, with additional information (e.g., a STROBE checklist and further details of the protocol) provided in the online Appendices.

Sample

Potential study participants were recruited *via* treating clinicians from a wide range of youth and adult secondary care services in Newcastle, England (e.g., early intervention, crisis assessment, etc.) between 2013-2016 (Appendix 1).

The key eligibility criteria were that the individual was aged 16 to 25, had sought help for at least one clinically significant mood episode within the last two years (e.g. a treated or untreated sub-threshold or clinically diagnosed depression), currently met one or more BAR criteria (Table 1), but had never experienced or been diagnosed with a hypomanic or manic episode (specifically, a treated or untreated episode of ≥ 4 days).

Other inclusion criteria were: The individual was (i) assessed as having mental capacity and (b) willing and able to provide written informed consent (with additional parent/guardian consent for those aged 16-18). Other exclusion criteria were: (i) a previous clinical diagnosis of BD I, BD II or severe borderline or antisocial personality disorder; (ii) past treatment with a mood stabilizer or antipsychotics for a mood episode; (iii) currently an inpatient at a mental health unit; (iv) clinically reported IQ below 70, or reading age, cognitive functioning or knowledge of English language preclude completion of screening or assessment interviews; (v) evidence of organic brain damage and/or a serious physical illness that precludes completion of assessment interviews (vi) currently subject to involuntary treatment under the Mental Health Act (e.g., community treatment order) or on probation with a requirement for treatment.

Assessments

All participants were invited to attend three interviews over 12 months (Appendix 1). Two baseline assessments explored demographics and clinical characteristics (including phenomenology, treatment history, etc.). The assessment of BAR criteria was undertaken using Structured Clinical Interviews for DSM IV (SCID parts 1 and 2) with the 'skip questions' removed to ensure subthreshold presentations were explored. Supplementary items evaluated other key features, e.g., family history of mental disorders in first degree relatives and probable antidepressant emergent elation (Appendix 2). The 12-month follow-up assessed the primary outcome (i.e., transition from at-risk state to full-threshold hypo/manic episode).

Selection of BAR criteria: Publications about BAR criteria indicate that some assessment tools comprise brief checklists, some offer more nuanced assessments of proximal risk factors (e.g., rating the quantity and severity of presenting symptoms), whilst others adopt a broader approach to BAR, incorporating a range of childhood factors (e.g., experiences of abuse, childhood anxiety, etc.). However, research demonstrates that many of the latter risk factors are not specific for BD [13]. So, for this study (targeting the peak age range for onset of BD), we focus on the BAR criteria that are most consistently reported in prior publications and are associated with a transition rate of about 25% (range 10-40%) over about 6 to 30 months. These criteria are primarily derived from the original BAR research and extended by other investigators; also, they incorporate key elements of clinical phenomenology described in other established tools [2,4,6,7]. Operationalization of these criteria are provided in Appendix 2.

Statistical analysis

The analyses used are based on classical approaches to evaluating the performance of different 'diagnostic' tests (in this study, the predictive validity of BAR criteria) and follow the principles of Bayes theorem (Appendix 3 gives further details). We employ Likelihood Ratios (LRs) to quantify the change in the certainty (for early transition) conferred by the presence or absence of different BAR criteria (alone or in combination). Essentially, a high positive LR (+LR) indicates a BAR criterion has very good ability to identify individuals who will experience early transition. In contrast, a low negative LR (-LR) suggests the absence of a particular BAR characteristic will substantially reduce the likelihood of early transition. The LR scan be used to estimate the diagnostic odds ratio (DOR= LR+/LR-). This single estimate can be used to compare the clinical utility of different BAR criteria for identifying risk of early transition (a higher DOR indicates greater discriminatory ability).

Lastly, the LR scan be used in conjunction with the pre-test probability of transition to estimate individual (post-test) probabilities of BD onset. To assist interpretation, we demonstrate how these research estimates of early transition to BD could be applied to

clinical settings. As an example, we show the clinical impact of e.g., a clinical decision that individuals with a transition probability ≥ 50% should be automatically offered treatment, whilst all those with a probability of >33% (but <50%) would be initially offered more frequent prospective monitoring, with decisions regarding more intensive intervention based on clinical judgement (presence of >1 BAR factor, a review of negative probabilities, etc.).

Results

The sample comprised 110 individuals with a mean age of 19.3 (SD 3.7). About 90% (n=98) were of European ancestry; 68% (n=75) were female; and 65% (n=72) were attending school or other education, training, or employment settings. Eighty individuals (73%) reported current or past exposure to antidepressants.

As shown in Table 1, whilst 34 (31%) participants met BAR criteria for subthreshold mania only eight (7%) met strict criteria for probable antidepressant induced elation. Assessment of specific symptoms revealed that hypersomnia was common (25%), whilst anergia was identified in 17%, and the combination of anergia and hypersomnia co-occurred in 15%. Many individuals met criteria for >1 BAR factor (Mean = 1.38, SD=0.51).

Table 1 about here at 12 months, 26 individuals (23.6%) demonstrated early transition to hypo/mania. The +LRs ranged from 1.08 (i.e., a small additional increase in probability of early transition) up to 5.38 (reported for individuals with the combination of cyclothymia, depression and a family history of BD in first degree relatives). Estimates of -LRs indicated that subthreshold mania had the lowest value (0.38). Overall, subthreshold mania has the highest DOR (9.56), closely followed by the combination of cyclothymia, depression and family history of BD (8.13).

Figure 1 shows the estimated positive and negative probabilities associated with each BAR criterion. Employing a treatment threshold of >50% would lead to three groups of individuals being offered immediate treatment (those with subthreshold mania; cyclothymia, depression and family history of BD; or anergia with/without hypersomnia). In contrast, nearly all individuals would be offered more frequent monitoring, except those who met BAR criteria for probable antidepressant induced elation or hypersomnia alone (who would receive routine follow-up).

Discussion

This study preferentially recruited youth who were identified by mental health professional as being at high risk of developing BD. The overall rate of early transition to hypo/mania (23.6%) was close to the assumed pre-test probability (25%). This rate matches early research findings, but is higher than some other studies [2,7]. This might be a consequence of recruitment bias in our study (e.g., if clinicians preferentially referred very high-risk youth to and/or selected those who met more than one BAR criteria). However, the variable rate of transition to BD across studies illustrates why LRs and Bayes theorem may be preferable to standard test measures e.g., sensitivity and specificity. The latter may be useful metrics for tests applied to older adults with established diagnoses but can be problematic when employed to evaluate the utility of BAR criteria in youth recruited across disparate community and clinical settings. Essentially, sensitivity and specificity estimates are independent of disease prevalence, but are dependent on disease severity [12]. In the early stages of BD, it can be difficult to differentiate between health and illness (so test sensitivity decreases) and are not the most informative measure of the predictive ability of a test [14].

There are several potential advantages to employing LRs in early intervention research. For example, reviewing the LRs for the BAR criteria demonstrates that these different signs and symptoms are not prognostically or diagnostically equivalent, especially if a 12-month cut off is applied. Notably, we confirm the importance of subthreshold mania as the presentation most associated with early transition, but also demonstrate that the presence of different combinations of BAR may identify individuals who are at higher than average risk e.g., the combination of cyclothymia, depression and family history of BD conferred increased risk compared with depression and family history or cyclothymia and family history alone (indicating that LRs can have multiple levels in individual participants). In contrast, hypersomnia was common and had a lower +LR (and higher -LR) than anergia alone or the combination of anergia and hypersomnia (so we can speculate that in a youth population that is known to have a high prevalence of hypersomnia, this feature may be less discriminatory than anergia alone or the atypical depression pattern of anergia and hypersomnia). McGee [15] and others suggest that LRs are probably the best measure of diagnostic/prognostic accuracy, but we note that limitations include concerns that wide confidence intervals undermine the ability to rule in or rule out disease and that in many clinical settings the utility of LRs partly depend on being able to estimate pretest probabilities. Alternatives to LR can include DOR. However, whilst the DOR estimates highlight the best trade-offs between +LR and -LR, they are difficult to apply clinically and

Table 1: Positive (+LR) and negative (-LR) likelihood ratios and Diagnostic Odds Ratios (DOR) for early transition to hypo/mania for each Bipolar-at-Risk (BAR) criterion.

BAR Criteria	Prevalence in Cohort (N=110)*	+LR (95% CI)	-LR (95% CI)	DOR (95% CI)
SUBT_MANIA	34 (31%)	3.63 (2.18, 6.05)	0.38 (0.21, 0.68)	9.56 (3.54, 25.87)
CYCLO_DEPN	23 (21%)	2.96 (1.49, 5.90)	0.67 (0.48, 0.95)	4.42 (1.64, 11.83)
FHxBD_DEPN	19 (17%)	1.88 (0.85, 4.29)	0.85 (0.66, 1.09)	2.21 (0.77, 6.38)
CYCLO_FHxBD_DEPN**	16 (15%)	5.38 (2.16, 13.4)	0.66 (0.49, 0.90)	8.13 (2.58, 25.56)
HYPERSOMNIA	27 (25%)	1.62 (.83, 4.26)	0.82 (0.63, 1.12)	1.94 (0.74, 5.08)
ANERGIA	19 (17%)	3.59 (1.64, 7.88)	0.69 (0.5, 0.94)	5.21 (1.82, 14.88)
HYPERSOMNIA_ANERGIA	16 (15%)	3.23 (1.35, 7.76)	0.77 (0.59, 1.00)	4.2 (1.39, 12.76)
PSYCHOTIC_Sx	21 (19%)	1.99 (0.93, 4.26)	0.82 (0.62, 1.08)	2.43 (0.87, 6.71)
ADM_ELATN	8 (7%)	1.08 (0.23, 5.02)	0.99 (0.88, 1.13)	1.09 (0.27, 5.65)

*Individuals could present with >1 BAR criterion, so column total exceeds cohort size; **Appendix 2 provides further explanation of this criterion; ADM_ELATN: Probable antidepressant emergent elation; ANERGIA: Anergia &/or fatigue; CYCLO_DEPN: Cyclothymia &Depression; FHxBD_DEPN: Family history of bipolar disorder in first degree relative &personal history of Depression; PSYCHOTIC_Sx: Psychotic symptoms; SUBT_MANIA: Sub-threshold mania

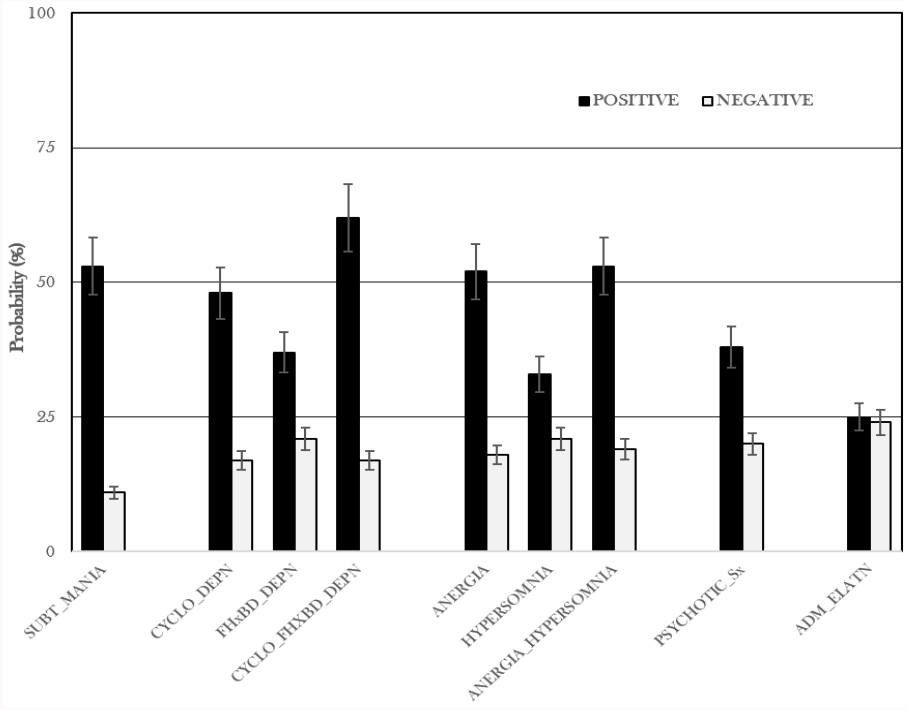

Figure 1: Probability of early transition to hypo/mania to likelihood ratios for each BAR criterion (see text for further detail).

probably have more utility in comparative research [12].

The final element of our study explored how LRs, and probabilistic reasoning might be applied clinically. Any proposal for developing early intervention services for youth at risk of developing BD will consider the economic cost *vs.* clinical benefit. So, it is helpful to predict the clinical impact associated with offering more intensive prospective monitoring to those at above average risk of BD onset and/or targeted early treatment to those at very high risk of developing BD (with LRs and probabilities indicating high levels of certainty about transition with limited risk of treating 'false positives'). We specifically chose the 12-month for early transition to BD as it is suggested that 6 to 18-month time frames are clinically informative, indicating the potential value of BAR screening and likely increase in workload associated with delaying/preventing transition (whereas 2 to 5-year follow-ups typically have more research utility). Of course, the quantitative clinical decision-making thresholds may be regarded as too low (certainly compared to general medical thresholds), but they serve to demonstrate how we might develop BAR research forward and expand the clinical relevance of BAR studies.

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