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Title: Number of episodes in bipolar disorder: The case for more thoughtful conceptualisation and measurement

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

Abstract

Objectives: Number of mood episodes (NoE) may be an important prognostic indicator in bipolar disorder, with implications for treatment. However, NoE has been conceptualised and measured inconsistently throughout the literature. This review examines the construct of NoE in bipolar disorder, with the aim of enhancing its conceptualisation and measurement.

Methods: A critical evaluation of literatures on important correlates of NoE, conceptually and phenomenologically overlapping features, and previous studies considering and measuring this construct was undertaken.

Results: The literature indicates that despite frequent use, NoE has been inconsistently defined and measured. Multiple studies have linked NoE with important clinical factors, including relapse, functioning, cognitive impairment, and the effectiveness of both pharmacological and psychosocial interventions, yet conclusions are limited by its inconsistent treatment. Additionally, it seems evident that that NoE may best be treated as a fuzzy construct (rather than precise figure), with yet to be defined overlaps with clinical variables such as age at onset and severity. Attempts to measure this construct have varied in comprehensiveness and structure.

Conclusions: The NoE construct may have important implications for individuals with bipolar disorders. However, more consistent and systematic definition and assessment of NoE is required to advance this literature and clarify its role. Recommendations aimed at advancing the conceptualisation and the measurement of NoE are provided.

Conceptualisation may be advanced by considering and exploring relationships between NoE and factors with which it overlaps, while measurement may best be improved with increased consistency and balancing accuracy with feasibility.

Key words

Bipolar

Bipolar Disorder/classification*

Bipolar Disorder/psychology

Models, Psychological*

Prognosis

Psychiatric Status Rating Scales

Disease Progression

Humans

The number of affective episodes an individual with bipolar disorder experiences is an important and under-recognised consideration in research and clinical practice. Accumulating mood episodes may have significant implications for individuals' illness experience, prognosis and treatment. The aim of this critical review is to highlight the potential clinical relevance of the construct of 'number of episodes' (NoE) experienced by individuals with bipolar disorder (BD), and encourage more careful conceptualisation and measurement of this construct. This review will begin with a discussion of important correlates of NoE in BD. The following section highlights the relevance of the NoE construct to investigations of clinical stage and neuroprogression in BD. Next, the review focuses on conceptual issues surrounding NoE, followed by an outline of key issues relating to efforts to measure NoE. Finally, recommendations for improving both the conceptualisation and measurement of NoE in BD are offered.

Correlates of number of episodes

NoE may be an important prognostic indicator in BD. Multiple studies have demonstrated associations between NoE and a range of important outcomes amongst people with BD. This section will examine the key correlates of NoE in BD, including its relationship to clinical and functional outcomes, and to response to psychosocial interventions and pharmacotherapy. Important caveats to interpreting these data are examined in a later section; therefore, in this section, NoE will be treated as a unified, quantifiable construct, reflecting its treatment in the literature. Issues with this approach will be discussed thereafter.

Longitudinal illness course. Accumulating episodes may increase risk of relapse and recurrence in BD. For example, a narrative review concluded that across studies, NoE is a

reliable predictor of relapse in BD ¹. More recently, within two longitudinal studies, NoE predicted risk of recurrence in the subsequent two- or four-year periods ^{2,3}. Similarly, a large naturalistic study reported an increased risk of relapse leading to hospitalisation with each subsequent episode ⁴. These findings were confirmed in a large epidemiological study, wherein NoE predicted further hospitalisations ⁵.

Illness features. NoE may also be related to worsening symptoms and illness features. In the large Systematic Treatment Enhancement Program (STEP-BD) sample, higher NoE at baseline was associated with a range of clinical factors, including more chronic and severe symptoms, higher levels of disability, and lower quality of life ⁶. These differences remained after 12 months of evidence-based pharmacological and psychological interventions. Subsequent analyses of the STEP-BD sample showed that those who had experienced at least ten mood episodes were slower to recover from episodes and more likely to report symptoms of sadness, anhedonia, euphoria, irritability and anxiety between episodes ³. In an epidemiological study, NoE was associated with a higher number of current and lifetime psychiatric and medical comorbidities ⁵. Studies have also reported higher rates of suicidality and higher levels of perceived stigma for those with higher NoE ^{3,5,7-9}.

Functioning. Individuals' functioning also appears to worsen with accumulating mood episodes. For example, past total, manic and depressive NoE have been shown to predict global functioning in those with BD ¹⁰⁻¹⁴. As noted earlier, Magalhaes, et al. ⁶ found that in the STEP-BD sample, having experienced more than ten episodes was a significant predictor of disability and reduced functioning. Similarly, the large European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study demonstrated that significantly fewer individuals reporting multiple episodes achieved functional recovery than those who had experienced a single episode (Tohen et al. 2010). Additionally, in the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) study, NoE was associated with increased likelihood of cross-sectionally reporting permanent disability, as well as prospective functional decline ⁵.

Specific domains of functional impairment have been linked with NoE. For example, in one study comparing functioning between those with multiple episodes versus one prior episode, the former group had worse functioning across the domains of autonomy, work, interpersonal relationships and cognitive functioning, and these differences were consistent over 12 months ¹³. Similar domains of impairment were reported in the NESARC study; higher rates of unemployment and role impairment and poorer social functioning at baseline

were associated with NoE ⁵. Within this study, prospective declines in these functional domains were predicted by NoE, across several years. In a small outpatient study, work and family role disability was predicted by number of manic episodes, and social role disability was predicted by number of depressive episodes ¹⁵. A further study demonstrated that for each manic episode experienced, participants were 1.4 times more likely to report poor work adjustment ¹⁶.

Findings are less straightforward in relation to the impact of NoE on cognitive functioning, partly due to methodological heterogeneity and study limitations. Multiple studies have linked NoE, especially manic episodes, with greater cognitive impairments, reporting differences across cognitive domains including executive function, psychomotor speed, cognitive flexibility, verbal processing and memory ¹⁷⁻²⁴. However, in a cross-sectional study, Nehra and colleagues ²⁵ reported poorer cognitive performance in a first episode group, relative to a multiple episode group. A few explanations may illuminate this inconsistency. In the latter study, those with multiple episodes had experienced an average of fewer than two manic episodes, lower than that reported in other studies (as shown in a later section). Additionally, less time spent euthymic since their last episode and increased likelihood of psychotic symptoms in the first episode group may explain their poorer cognitive performance, given associations between these characteristics and cognitive functioning ^{26,27}. A related finding is that individuals' risk of developing dementia appears to increase with accumulating NoE in BD, with one study reporting that each episode incurs a 6 per cent increase in likelihood of developing dementia ²⁸. Taken together, despite some inconsistencies, there appears to be an association between NoE and poorer cognitive functioning.

Treatment response. NoE has been linked with reduced treatment response, however the type of treatment appears important. For example, a meta-analysis of Olanzapine trials found that those with fewer NoE were consistently more likely to respond to Olanzapine when manic or depressed, and experienced improved relapse rates ²⁹. Similarly, some studies have reported superior response to Lithium during mania in those with fewer NoE ³⁰⁻³², and others have reported superior prophylaxis with fewer NoE ³³. However, a comprehensive systematic review and subsequent meta-analysis failed to support these findings ^{34,35}, suggesting that the weight of the evidence indicates that NoE has little role in the effectiveness of Lithium. Differences in findings may be attributable to differences in sample characteristics and outcome measures; for example, treatment adherence was not controlled,

and participant mood states and outcomes varied. Conclusions for antidepressant medications are also unclear, with some studies suggesting that NoE predicts response to antidepressants³⁶ and others finding no differential effectiveness based on NoE^{6,37}. Again, these differences may reflect uncontrolled sample characteristics (polytherapy, NoE distribution and mood states). It appears that some medications may be more effective for those with fewer NoE, while differential effectiveness is not evident for others. NoE has also been associated with reduced medication adherence, further impacting treatment outcomes and research conclusions^{38,39}.

Turning to psychotherapy outcomes for BD, a more consistent pattern of findings in relation to NoE emerges, with a handful of studies comparing intervention outcomes based on NoE. For example, post hoc analyses of Scott et al.'s pragmatic effectiveness trial of cognitive behavioural therapy (CBT)⁴⁰ suggested that only those with 11 or fewer episodes benefitted. Similarly, post hoc analyses of a group psychoeducation trial showed that, following psychoeducation, those with greater NoE reported less time to recurrence and more time spent in manic, hypomanic, mixed and depressive episodes⁴¹. In another psychoeducation trial, individuals were classified into stages of illness and those considered to be within an earlier stage of illness (with lower NoE) experienced longer time to recurrence following caregiver psychoeducation, while no benefits were reported for those with higher NoE⁴². Results from the STEP-BD trial of psychosocial interventions are consistent with these data. For example, those with lower NoE were more likely to (1) respond to psychotherapies (CBT, interpersonal and social rhythm therapy, family-focused therapy and collaborative care), and (2) achieve recovery and respond to all interventions more quickly⁸. Additionally, those with fewer episodes responded similarly across interventions, while those with higher NoE had better results from more intensive interventions. Overall, study findings to date suggest that adjunctive psychotherapy may be less effective for those who have experienced greater NoE. However, it should be noted that there are issues with circularity when considering episode relapse and recurrence as evidence of intervention effectiveness in the context of NoE.

In sum, there is substantial (albeit not unequivocal) evidence for an association between greater NoE and important features of BD including relapse risk, illness course, clinical and functioning parameters, and treatment response. As suggested by Scott et al.'s highly cited CBT for BD outcome study⁴⁰ (where post hoc analyses found a bifurcation in

response at 12 episodes), the NoE construct clearly warrants more systematic attention in BD research and treatment.

NoE: Theoretical importance

The relationship between NoE and worsening clinical and functional outcomes has been explained by neuroprogression and clinical staging hypotheses. Because of this link, and in the absence of established markers of clinical staging in BD, many studies aim to employ NoE as a “proxy” of stage ^{6,29,43,44}. This section will review the relevance of the NoE construct within the literature on neuroprogression and clinical staging.

Staging and Neuroprogression Staging and neuroprogression are linked, yet distinct, theoretical processes explaining illness progression in BD, and NoE may have an important role in both. Neuroprogression posits that accumulating episode recurrences lead to increased pathological processes and decreased protective processes within the brain ⁴⁵; specifically, increased inflammation and sensitisation, decreased neurotrophins and cumulative alterations within the brain ⁴⁶⁻⁴⁸; As summarised by Post (2010), there is considerable support in the literature for chemical and structural brain changes linked with increasing NoE. Specifically, increased ventricle volumes and decreased volume of the hippocampus and corpus callosum, as well as reduction in grey matter volume in several regions have been associated with accumulating NoE ^{43,49-53}.

Biochemical evidence, while scarce, broadly concords with structural data. For example, Grande, et al. ⁵⁴ clustered individuals based on NoE, functioning, duration of illness, and age at onset. The resultant two clusters could be differentiated by levels of the cytokine IL-6. However, these results are yet to be replicated ⁵⁵. A further implicated process is that of oxidative stress, wherein an imbalance of oxidants and antioxidants leads to epigenetic changes. An association between NoE and oxidative stress has been demonstrated in BD, with individuals with higher NoE demonstrating elevated antioxidant enzymes, pointing to altered oxidative processes ⁵⁶. Therefore, biochemistry may change with increasing NoE in BD, but insufficient data exists to demonstrate how this is linked with episode recurrences.

Clinical staging in psychiatry presumes that, for a proportion of individuals, mental illnesses follow a predictable, progressive trajectory. Specific staging models have been proposed for BD and, while these are yet to be adequately validated, are widely considered to be of heuristic value ⁵⁷⁻⁵⁹. NoE has been described as both a feature and an explanatory factor

in clinical staging of BD. NoE may be causally related to the functional and clinical sequelae of advancing illness stages⁶⁰. Mood episodes have been associated with systemic toxicity, and in addition to the potential neurological impacts, may lead to functional and clinical changes associated with progression through clinical stages^{61,62}. This appears to have face validity with consumers; for example, individuals with higher NoE are more likely to perceive that they have experienced ‘illness progression’⁶³. Further, as predicted by sensitisation and kindling models, initial episodes are likely to be precipitated by environmental triggers and stressors, while later episodes may occur without exogenous precipitants, implying sensitisation of mood regulatory structures via structural, chemical and functional changes^{45,47,64}.

While the literature regarding clinical staging and neuroprogression in BD is still maturing, NoE is frequently employed as a marker or proxy of stage and therefore optimising the assessment of NoE may in turn advance this literature.

The construct of NoE: Conceptual issues

The consideration of NoE is complicated by the complex and heterogeneous presentations of BD, and by factors which overlap conceptually and phenomenologically with NoE. For example, related illness features such as rapid cycling, predominant polarity and duration of illness complicate the exploration of NoE. In addition, definitional issues contribute further to heterogeneity; including definition of episodes, onset and offset, recurrence and relapse. Conceptual issues related to the construct of NoE, as illustrated in Figure 1, are introduced in this section.

By definition, individuals with rapid cycling BD experience higher NoE than non-rapid cyclers; around seven times as many manic and twice to three times as many depressive episodes^{65,66}, adding to the overall burden. Rapid cycling is also linked with poorer outcomes, and it is difficult to disentangle impacts associated with accumulating NoE alone from those related to episodic frequency^{66,67}. Further, rapid cycling is typically a transitory phenomenon^{66,68}, adding to attribution difficulties. Despite this complexity, research exploring the impact of NoE has demonstrated that these effects cannot be wholly accounted for by rapid cycling; for example differences in Lithium responsiveness based on NoE were independent of rapid cycling status³². Therefore, rapid cycling status may be a related, yet separable, construct to NoE, with the precise contribution of each as yet difficult to ascertain. Similarly, an individual’s total illness duration, their duration of untreated illness, and the age

at which they experienced their initial mood episode have each been linked with poorer outcomes in BD, and each interacts with NoE ⁶⁹⁻⁷¹. Research is yet to untangle the relative contributions of each with relation to NoE, and this will be an important direction for future research.

Further, it appears likely that manic, hypomanic and depressive episodes may have different impacts, and therefore that the proportion of each (an individual's 'predominant polarity') is relevant to the role of NoE ^{15,72}. Some studies have found episodes of one pole to be more strongly associated with specific outcomes. For example, several studies have reported that manic episodes, but not depressive episodes, are associated with poorer cognitive function ^{16,17}. In addition, work and familial functioning were related to manic NoE, while social functioning was related to depressive NoE in one study ¹⁵. However, the relative impacts of episodes of different types is still largely unknown ⁷².

Careful assessment and documentation of these overlapping constructs, as illustrated in Figure 2, will contribute to illuminating their interrelationships and advancing the understanding of the role of NoE. However, regardless of whether future research in this area indicates that NoE imparts unique impact over and above the role of illness factors such as those described above, NoE may nonetheless represent a useful proxy for illness progression.

Additionally, across various studies, differing definitions of NoE and of episode-related constructs have been used. For example, hypomania has been variously defined as periods of at least 2 days ⁷³ to at least 7 days ^{8,74,75}, while others fail to report whether mixed or hypomanic episodes have been included when reporting NoE ^{11,16}, with such differences potentially influencing conclusions. Changes within major diagnostic classification systems also have the potential to influence episode classification and counts. For example, mixed episodes are typically classified as manic or elevated episodes, however the latest Diagnostic and Statistical Manual (DSM-5) ⁷⁶ introduced a 'with mixed features' specifier which can apply to manic or depressive episodes, rather than a separate episode type.

The construct of NoE: Measurement issues

Given its potential importance, with NoE being increasingly discussed in the literature, establishing methods to maximise the reliability of measurement while balancing feasibility is required. This section summarises measurement issues associated with NoE, drawing from published research and existing measurement tools.

Assessment methods. A number of methods have been employed to date to gather information relevant to NoE, and these are summarised in Table 1. [Table 1 about here]. Many studies considering NoE fail to define or disclose their definition or method of assessment of NoE ^{9,31,40,41,44}. When methods of assessment are disclosed, these range widely in degree of structure, burden on participants, and comprehensiveness.

For example, some studies have collated episode histories from various sources, such as clinical case histories, hospital records and family members e.g. ^{7,11,74,77}. When an extensive clinical history is available and its use is practical, benefits can include improved accuracy. However, for both research and clinical purposes this is often unfeasible, and as such, measures which balance pragmatics with maximising precision may be preferable.

In the absence of medical history documents, participants are often asked to recall their lifetime mood episodes with varying prompts, and existing instruments have been used or tailored for this purpose. Specifically, the current editions of the Mini International Neuropsychiatric Interview (MINI) ⁷⁸(version 7.0.2) and the Structured Clinical Interview for the DSM (SCID-5-RV) ^{79,80}, each contain a question regarding depressive NoE (see Appendix A), but not specifically manic nor hypomanic NoE. Several studies report using or adapting these instruments to quantify NoE ^{10,16}, and others have used a combination of these and the previously described methods ^{11,74,77}. The Affective Disorders Evaluation (ADE) is another tool used for gathering data about NoE, created and implemented by the STEP-BD group ^{5,6,8,75,81}. The ADE includes a question per episode type, aided by prior questions elucidating interviewees' symptoms. Further, the NIMH Life Chart Method (NIMH-LCM) involves graphing mood shifts including episodes above (hypo/mania) and below (depression) a dateline, with manualised prompts. The NIMH-LCM has been used in several studies ^{22,82}, however, while it was developed for both retrospective and prospective use, it has only been validated prospectively, limiting its applicability for retrospective recall ^{83,84}.

Retrospective assessment issues. Retrospective recall is inherently problematic and subject to heuristic biases, particularly for emotionally salient psychological phenomena ^{85,86}. In addition, a key issue with retrospective assessment methods is that many individuals with BD experience autobiographical memory difficulties, most commonly overgeneral autobiographical memory ^{24,87-89}. These difficulties are compounded by greater numbers of previous episodes ^{74,87}, and cognitive and memory impairments are most prominent during episodes, impacting the recall thereof ¹⁷. Martino, et al. ⁷⁴ compared subjective recall of

episodes with clinician rated episodes over periods of 2 to 6 years, finding less than 20 per cent concordance. In most cases, episodes were underreported by individuals with BD, averaging 2.74 episodes (58%) over the study period. This may reflect a broader underestimation of NoE based on self-report methods, resulting in a systematic underestimation of NoE. Table 2 compares data from a number of studies reporting on the NoE construct.

[Table 2 about here]

Burden on individuals with BD. Being asked to recall details of often traumatic and disruptive mood episodes is likely to be distressing for many individuals with BD. Lengthy and overly intrusive assessment may impact individual's motivation to engage with assessment and provide accurate information. Structured assessment methods may result in more accurate recall and reduced burden.

Assessing the NoE an individual with BD has experienced is therefore likely to have significant implications for treatment and research. While various methods have been employed for this purpose, assessment largely appears to be perfunctory, with far less attention paid than to other important clinical factors, such as symptom severity. The definition and measurement of episodes varies between studies, with differences in researchers' definitions and operationalisations of episodes themselves, onset and offset, recurrence and relapse. As a result, comparisons between studies are imprecise, rendering conclusions about the specific role of NoE tenuous. This implies a need for more reliable and precise measurement of NoE. On the other hand, given evidence that individuals' self-reported NoE is linked with important clinical and functional outcomes (e.g. ⁶), the burden associated with collating medical histories and informant reports and the distress which may result from such examinations, efforts may be better spent enhancing self-reported recall methods, balancing feasibility with precision. Without transparent and replicable assessment methods, the relationship between NoE and clinical and prognostic factors will remain slippery.

Where to from here?

In order to progress the understanding of the role of NoE in the experiences and treatment of individuals with BD, more rigorous consideration of this construct is necessary. Several tools exist which can be used to gather information about NoE, but these are inconsistent in their definition of episodes and the methods used to aid the recall of this

information. Our aim here is to support future research by offering provisional guidance towards consistent, feasible and accurate measurement of NoE, derived from a review of the literature. Accordingly, a discussion of key recommendations follows and these are summarised in Box 1.

Towards an improved understanding of NoE

Explicit operationalisation. At a minimum, studies considering NoE ought to disclose their definition and the process used to gather this information. Standard definition of episodes by type (manic, hypomanic, mixed and depressive), and of related constructs including recurrence, relapse and remission are required for consistency across studies. Appropriate definitions are provided in an International Society of Bipolar Disorders report⁹⁰, and compatible working group report⁹¹, and are best supported by internationally recognised diagnostic criteria, as in the Diagnostic and Statistical Manual of Mental Disorders⁷⁶ or the International Classification of Diseases. These are summarised in Table 3. Further, there is preliminary support for the possibility that episodes of different types may have different impacts, and so separate reporting of total, manic, hypomanic, mixed and depressive episodes is recommended in order to advance this understanding.

Documentation of overlapping phenomena. Future research will benefit from assessing and reporting the various course of illness variables which overlap with NoE. As shown in Figure 2, the various phenomena related to both NoE and important outcomes in BD, such as duration of illness, age of onset, and rapid cycling, complicate the understanding of the role of NoE. The first step towards improving our understanding of such relationships is the consistent assessment and reporting of these phenomena. Subsequently, further clarification may be offered by carefully designed studies which aim to untangle the role of these factors.

NoE and staging. Despite NoE likely representing an oversimplification of clinical staging phenomena, with episodic parameters speculative, NoE is currently the best candidate for the operationalisation of clinical staging in BD^{6,92}. Additionally, this operationalisation has clinical relevance and face validity, and is (theoretically) relatively simple to assess. However, there are issues associated with its use in this context. In addition to the assessment issues already described, if assessment of NoE is employed as a proxy of stage within research contexts, ideally, it should be considered within the context of the individual, with additional factors which contribute to the assessment of ‘stage of illness’ (such as functional

and neurocognitive decline), and factors which may confound it (such as rapid cycling, age of onset and duration of illness) informing such assessments and addressing issues of reductionism and circularity.

Research agenda. This review has illuminated some key areas for future research. Firstly, while a range of tools are currently available to assess the construct of NoE, none has been extensively validated or compared for this purpose and as such, further research is required to evaluate existing tools and/or develop a new measure for the assessment of NoE. Research designs which would advance this issue would directly compare the psychometric properties and predictive validity of multiple (available or newly-designed) measures of NoE. In addition, more research assessing the relationship between episodes of different types and i) important clinical outcomes and ii) overlapping phenomena is needed. For example, employing measures which gather data about different episode types and modelling their relationships with important clinical outcomes to assess the contribution and differential impacts of each would constitute a valuable next step. Similarly, as noted, studies assessing overlapping constructs alongside NoE (as in Figure 2) and controlling for these or evaluating their relative predictive validity for key outcomes or prognostic indicators may contribute to untangling the relationships between, and relative clinical utility of, these phenomena.

Towards improved measurement of NoE

Consistent measurement. Assessment supported by collateral history has benefits, however self-reported NoE has been linked with various clinical and functional correlates. Neither has been utilised and documented consistently in the literature. Therefore, establishing and documenting consistent methods for assessing this construct are necessary. Ultimately, replicable, standardised assessment methods will vastly improve the heterogeneity present in the literature and the understanding of the implications of NoE.

Balancing feasibility and accuracy. As highlighted in this review, methods of assessment for NoE vary widely, and many of these, such as collating medical and case histories, appear unfeasible for use in the contexts in which NoE is likely to be of most use (such as clinical practice). In addition, prolonged and detailed recollection of episodes is likely to be distressing for individuals with BD, and there is no evidence to suggest that this leads to more accurate episode recall. It appears likely that individuals systematically underestimate their NoE and that those with greater NoE may count with even less accuracy. In sum, we propose that NoE may best be treated as a fuzzy concept, rather than a precise datum and therefore efforts to achieve a reliable, feasibly attained 'estimate' of NoE may be

more important than efforts to derive a precise figure. Therefore, we suggest that future assessment attempts should pay more attention to minimising burden and achieving increased consistency, rather than greater precision.

Structured assessment methods. Self-report assessment methods adopted to assess NoE vary in their degree of structure and the types of prompts offered (see Table 1). Structured assessment methods are frequently employed in psychological assessment to aid recall and contribute to standardisation of clinical assessments, with well-documented heuristic biases (such as mood-congruence) less impactful in structured formats⁹³. In addition, structured assessment methods may reduce burden on participants. Therefore, developing structured methods to support the recall of NoE is likely to improve the reliability of assessment while reducing burden on individuals.

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[Table 3 about here]

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To advance the assessment of NoE, it is useful to draw parallels with other phenomena that rely upon memory of distal past events and may induce discomfort. For example, we know that asking about specific types of traumatic events generates more reliable recall than asking omnibus questions about ever having experienced trauma across one's lifetime⁹⁴ and the same may hold true for the assessment of NoE. In addition to a structured approach, providing a simple definition of each type of episode being assessed and prompts to assist with recall are suggested. Examples of potential questions and prompts for each type of episode are provided in Appendix B. For example, some respondents may focus only on those episodes which led to hospitalisation, and timeline-based prompts may assist with recalling other episodes. These examples are based on the methods employed in two recent RCTs for which NoE was an inclusion criterion, however they have not been validated⁷³. In addition, given the potential for distress associated with the recall of mood episodes, advising respondents about this potential and ways to manage this (such as ceasing the assessment), while monitoring the impacts of the assessment is recommended (see Appendix B). Finally, to assist with comparability across measures and studies, number of episodes per type and in total should be recorded as a continuous (rather than categorical) metric.

[Box 1 about here]

Conclusion

NoE is a prognostic indicator in BD. Additionally, NoE has the potential to shape interventions and assist clinicians to tailor interventions to increase their effectiveness and reduce delays to accessing optimally effective interventions. NoE also informs clinical staging models in BD, offering an initial step towards operationalising the complex staging phenomenon, which is yet to be adequately translated into applied research with validated assessment tools. Therefore, efforts to improve its assessment have the potential to offer substantial benefits. Despite this, measurement of NoE to date has been inconsistent, with varying definitions and methods utilised and reporting sporadic. The various methods for assessing NoE employed have relative strengths and limitations. Self-reported NoE supported by consistent prompts appears to be a promising and feasible method; in future this could be supported by a standard structured interview. In addition, recommendations drawn from this review include consistent, evidence-based and transparent operationalisation and due consideration of factors which may interact with or confound NoE, in particular duration of illness, number of hospitalisations, rapid cycling, and predominant polarity.

References

1. Altman S, Haeri S, Cohen LJ, et al. Predictors of relapse in bipolar disorder: A review. *Journal of Psychiatric Practice*®. 2006;12(5):269-282.
2. Tundo A, Musetti L, Benedetti A, et al. Predictors of recurrence during long-term treatment of bipolar i and ii disorders. A 4 year prospective naturalistic study. *J Affect Disord*. 2018;225:123-128.
3. Park DY, Do D, Chang L, et al. Episode accumulation associated with hastened recurrence and delayed recovery in bipolar disorder. *J Affect Disord*. 2018;227:657-664.
4. Kessing LV, Hansen MG, Andersen PK. Course of illness in depressive and bipolar disorders. Naturalistic study, 1994-1999. *Br J Psychiatry*. 2004;185:372-377.
5. Peters AT, West AE, Eisner L, Baek J, Deckersbach T. The burden of repeated mood episodes in bipolar i disorder: Results from the national epidemiological survey on alcohol and related conditions. *J Nerv Ment Dis*. 2016;204(2):87-94.
6. Magalhaes PV, Dodd S, Nierenberg AA, Berk M. Cumulative morbidity and prognostic staging of illness in the systematic treatment enhancement program for bipolar disorder (step-bd). *Aust N Z J Psychiatry*. 2012;46(11):1058-1067.
7. Jimenez E, Arias B, Mitjans M, et al. Clinical features, impulsivity, temperament and functioning and their role in suicidality in patients with bipolar disorder. *Acta Psychiatr Scand*. 2016;133(4):266-276.
8. Peters A, Sylvia LG, Magalhaes PV, et al. Age at onset, course of illness and response to psychotherapy in bipolar disorder: Results from the systematic treatment enhancement program for bipolar disorder (step-bd). *Psychol Med*. 2014;44(16):3455-3467.
9. Vazquez GH, Kapczinski F, Magalhaes PV, et al. Stigma and functioning in patients with bipolar disorder. *J Affect Disord*. 2011;130(1-2):323-327.
10. Soni A, Singh P, Shah R, Bagotia S. Impact of cognition and clinical factors on functional outcome in patients with bipolar disorder. *East Asian Arch Psychiatry*. 2017;27(1):26-34.
11. MacQueen GM, Young LT, Robb JC, Marriott M, Cooke RG, Joffe RT. Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. *Acta Psychiatr Scand*. 2000;101(5):374-381.
12. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: A longitudinal follow-up study. *Am J Psychiatry*. 1995;152.
13. Rosa AR, Gonzalez-Ortega I, Gonzalez-Pinto A, et al. One-year psychosocial functioning in patients in the early vs. Late stage of bipolar disorder. *Acta Psychiatr Scand*. 2012;125(4):335-341.
14. Bonnin CM, Reinares M, Hidalgo-Mazzei D, et al. Predictors of functional outcome after a manic episode. *J Affect Disord*. 2015;182(C):121-125.

15. Gutierrez-Rojas L, Jurado D, Gurpegui M. Factors associated with work, social life and family life disability in bipolar disorder patients. *Psychiatry Res.* 2011;186(2-3):254-260.
16. Bonnín C, Torrent C, Goikolea J, et al. The impact of repeated manic episodes and executive dysfunction on work adjustment in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci.* 2014;264(3):247-254.
17. Martínez-Arán A, Vieta E, Reinares M, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry.* 2004;161(2):262-270.
18. Bourne C, Aydemir O, Balanza-Martinez V, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: An individual patient data meta-analysis. *Acta Psychiatr Scand.* 2013;128(3):149-162.
19. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: A systematic review of cross-sectional evidence. *Bipolar Disord.* 2006;8(2):103-116.
20. Lopez-Jaramillo C, Lopera-Vasquez J, Gallo A, et al. Effects of recurrence on the cognitive performance of patients with bipolar disorder: Implications for relapse prevention and treatment adherence. *Bipolar Disord.* 2010;12(5):557-567.
21. El-Badri SM, Ashton CH, Moore PB, Marsh VR, Ferrier IN. Electrophysiological and cognitive function in young euthymic patients with bipolar affective disorder. *Bipolar Disord.* 2001;3(2):79-87.
22. Denicoff KD, Ali SO, Mirsky AF, et al. Relationship between prior course of illness and neuropsychological functioning in patients with bipolar disorder. *J Affect Disord.* 1999;56(1):67-73.
23. Zubietta J-K, Huguelet P, O'Neil RL, Giordani BJ. Cognitive function in euthymic bipolar disorder. *Psychiatry Res.* 2001;102(1):9-20.
24. Scott J, Stanton B, Garland A, Ferrier IN. Cognitive vulnerability in patients with bipolar disorder. *Psychol Med.* 2000;30(2):467-472.
25. Nehra R, Chakrabarti S, Pradhan BK, Khehra N. Comparison of cognitive functions between first- and multi-episode bipolar affective disorders. *J Affect Disord.* 2006;93(1-3):185-192.
26. Torres JJ, Kozicky J, Popuri S, et al. 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. *Bipolar Disord.* 2014;16(2):159-171.
27. Levy B, Medina AM, Weiss RD. Cognitive and psychosocial functioning in bipolar disorder with and without psychosis during early remission from an acute mood episode: A comparative longitudinal study. *Compr Psychiatry.* 2013;54(6):618-626.
28. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *Journal of Neurology, Neurosurgery & Psychiatry.* 2004;75(12):1662.

29. Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord.* 2011;13(1):87-98.
30. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. *Am J Psychiatry.* 1999;156(8):1264-1266.
31. Maj M, Pirozzi R, Magliano L, Bartoli L. Long-term outcome of lithium prophylaxis in bipolar disorder: A 5-year prospective study of 402 patients at a lithium clinic. *Am J Psychiatry.* 1998;155(1):30-35.
32. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Mania: Differential effects of previous depressive and manic episodes on response to treatment. *Acta Psychiatr Scand.* 2000;101(6):444-451.
33. Kulhara P, Basu D, Mattoo SK, Sharan P, Chopra R. Lithium prophylaxis of recurrent bipolar affective disorder: Long-term outcome and its psychosocial correlates. *J Affect Disord.* 1999;54(1-2):87-96.
34. Kleindienst N, Engel RR, Greil W. Which clinical factors predict response to prophylactic lithium? A systematic review for bipolar disorders. *Bipolar Disord.* 2005;7(5):404-417.
35. Bratti IM, Baldessarini RJ, Baethge C, Tondo L. Pretreatment episode count and response to lithium treatment in manic-depressive illness. *Harvard Review of Psychiatry (Taylor & Francis Ltd).* 2003;11(5):245.
36. Pacchiarotti I, Valenti M, Bonnin CM, et al. Factors associated with initial treatment response with antidepressants in bipolar disorder. *Eur Neuropsychopharmacol.* 2011;21(5):362-369.
37. Baldessarini RJ, Tondo L, Visioli C, Vázquez GH. Illness history: Not associated with remission during treatment of major depression in 515 mood disorder patients. *J Affect Disord.* 2016;191:118-122.
38. Martinez-Aran A, Scott J, Colom F, et al. Treatment nonadherence and neurocognitive impairment in bipolar disorder. *The Journal of Clinical Psychiatry.* 2009;70(7):1017-1023.
39. Navarro S, Rodríguez F, Acosta FJ, García-Bello M. Variables associated with nonadherence in clinically stable patients with bipolar disorder. *Actas espanolas de psiquiatria.* 2016;44(5):157.
40. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: Randomised controlled trial. *Br J Psychiatry.* 2006;188(4):313-320.
41. Colom F, Reinares M, Pacchiarotti I, et al. Has number of previous episodes any effect on response to group psychoeducation in bipolar patients? A 5-year follow-up post hoc analysis. *Acta Neuropsychiatr.* 2010;22(2):50-53.
42. Reinares M, Colom F, Rosa AR, et al. The impact of staging bipolar disorder on treatment outcome of family psychoeducation. *J Affect Disord.* 2010;123(1-3):81-86.

43. Lavagnino L, Cao B, Mwangi B, et al. Changes in the corpus callosum in women with late-stage bipolar disorder. *Acta Psychiatr Scand*. 2015;131(6):458-464.
44. Murray G, Leitan ND, Berk M, et al. Online mindfulness-based intervention for late-stage bipolar disorder: Pilot evidence for feasibility and effectiveness. *J Affect Disord*. 2015;178:46-51.
45. Post RM. Mechanisms of illness progression in the recurrent affective disorders. *Neurotox Res*. 2010;18(3-4):256-271.
46. Berk M, Berk L, Dodd S, et al. Stage managing bipolar disorder. *Bipolar Disord*. 2014;16(5):471-477.
47. Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci Biobehav Rev*. 2007;31(6):858-873.
48. Fernandes BS, Berk M. Staging in bipolar disorder: One step closer to precision psychiatry. *Braz J Psychiatry*. 2017;39(2):88-89.
49. Kapczinski F, Dias VV, Kauer-Sant'Anna M, et al. The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(8):1366-1371.
50. Lisy ME, Jarvis KB, DelBello MP, et al. Progressive neurostructural changes in adolescent and adult patients with bipolar disorder. *Bipolar Disord*. 2011;13(4):396-405.
51. Kozicky JM, McGirr A, Bond DJ, et al. Neuroprogression and episode recurrence in bipolar I disorder: A study of gray matter volume changes in first-episode mania and association with clinical outcome. *Bipolar Disord*. 2016;18(6):511-519.
52. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. *Acta Psychiatr Scand*. 2016;134(2):91-103.
53. Cao B, Passos IC, Mwangi B, et al. Hippocampal volume and verbal memory performance in late-stage bipolar disorder. *J Psychiatr Res*. 2016;73:102-107.
54. Grande I, Magalhaes PV, Chendo I, et al. Staging bipolar disorder: Clinical, biochemical, and functional correlates. *Acta Psychiatr Scand*. 2014;129(6):437-444.
55. Siwek M, Sowa-Kucma M, Styczen K, et al. Associations of serum cytokine receptor levels with melancholia, staging of illness, depressive and manic phases, and severity of depression in bipolar disorder. *Mol Neurobiol*. 2017;54(8):5883-5893.
56. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev*. 2011;35(3):804-817.
57. Kapczinski F, Dias VV, Kauer-Sant'Anna M, et al. Clinical implications of a staging model for bipolar disorders. *Expert Rev Neurother*. 2009;9(7):957-966.
58. Berk M, Conus P, Lucas N, et al. Setting the stage: From prodrome to treatment resistance in bipolar disorder. *Bipolar Disord*. 2007;9(7):671-678.

59. Kapczinski F, Magalhaes PV, Balanza-Martinez V, et al. Staging systems in bipolar disorder: An international society for bipolar disorders task force report. *Acta Psychiatr Scand*. 2014;130(5):354-363.
60. Fries GR, Pfaffenseller B, Stertz L, et al. Staging and neuroprogression in bipolar disorder. *Curr Psychiatry Rep*. 2012;14(6):667-675.
61. Kapczinski F, Dal-Pizzol F, Teixeira AL, et al. A systemic toxicity index developed to assess peripheral changes in mood episodes. *Mol Psychiatry*. 2010;15(8):784-786.
62. Post RM, Fleming J, Kapczinski F. Neurobiological correlates of illness progression in the recurrent affective disorders. *J Psychiatr Res*. 2012;46(5):561-573.
63. Post RM, Altshuler LL, Leverich GS, et al. Illness progression as a function of independent and accumulating poor prognosis factors in outpatients with bipolar disorder in the united states. *Prim Care Companion CNS Disord*. 2014;16(6):10.4088/PCC.4014m01677.
64. Post RM, Weiss SRB, Leverich GS, Smith M, Zhang L-X. Sensitization and kindling-like phenomena in bipolar disorder: Implications for psychopharmacology. *Clin Neurosci Res*. 2001;1(1-2):69-81.
65. Kupka RW, Luckenbaugh DA, Post RM, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. *Am J Psychiatry*. 2005;162(7):1273-1280.
66. Gigante AD, Barenboim IY, Dias RD, et al. Psychiatric and clinical correlates of rapid cycling bipolar disorder: A cross-sectional study. *Braz J Psychiatry*. 2016;38(4):270-274.
67. Coryell W, Solomon D, Turvey C, et al. The long-term course of rapid-cycling bipolar disorder. *Arch Gen Psychiatry*. 2003;60(9):914-920.
68. Carvalho AF, Dimellis D, Gonda X, Vieta E, McLntyre RS, Fountoulakis KN. Rapid cycling in bipolar disorder: A systematic review. *J Clin Psychiatry*. 2014;75(6):e578-586.
69. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. Late-stage bipolar disorder. *Int J Neuropsychopharmacol*. 2009;12(4):447-458.
70. Post RM, Leverich GS, Kupka RW, et al. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. *J Clin Psychiatry*. 2010;71(7):864-872.
71. Altamura AC, Buoli M, Caldiroli A, et al. Misdiagnosis, duration of untreated illness (dui) and outcome in bipolar patients with psychotic symptoms: A naturalistic study. *J Affect Disord*. 2015;182:70-75.
72. Sanchez-Moreno J, Bonnin CM, Gonzalez-Pinto A, et al. Factors associated with poor functional outcome in bipolar disorder: Sociodemographic, clinical, and neurocognitive variables. *Acta Psychiatr Scand*. 2018.

73. Fletcher K, Foley F, Thomas N, et al. Web-based intervention to improve quality of life in late stage bipolar disorder (orbit): Randomised controlled trial protocol. *BMC Psychiatry*. 2018;18(1):221.
74. Martino DJ, Marengo E, Igoa A, Scapola M, Urtueta-Baamonde M, Strejilevich SA. Accuracy of the number of previous episodes reported by patients with bipolar disorder. *Compr Psychiatry*. 2016;65:122-127.
75. Deckersbach T, Peters AT, Sylvia LG, et al. A cluster analytic approach to identifying predictors and moderators of psychosocial treatment for bipolar depression: Results from step-bd. *J Affect Disord*. 2016;203:152-157.
76. Association AP. *Diagnostic and statistical manual of mental disorders : Dsm-5*. 2013.
77. Rosa AR, Reinares M, Michalak EE, et al. Functional impairment and disability across mood states in bipolar disorder. *Value Health*. 2010;13(8):984-988.
78. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The mini-international neuropsychiatric interview (m.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for dsm-iv and icd-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33;quiz 34-57.
79. First MB, Gibbon M. *Structured clinical interview for dsm-iv axis i disorders*. American Psychiatric Press Inc: Washington DC; 1997.
80. First MB. Structured clinical interview for the dsm (scid). In: *The encyclopedia of clinical psychology*. John Wiley & Sons, Inc.; 2014.
81. Sachs GS. Strategies for improving treatment of bipolar disorder: Integration of measurement and management. *Acta Psychiatr Scand Suppl*. 2004;110(422):7-17.
82. Honig A, Hendriks CH, Akkerhuis GW, Nolen WA. Usefulness of the retrospective life-chart method manual in outpatients with a mood disorder: A feasibility study. *Patient Educ Couns*. 2001;43(1):43-48.
83. Denicoff KD, Smith-Jackson EE, Disney ER, Suddath RL, Leverich GS, Post RM. Preliminary evidence of the reliability and validity of the prospective life-chart methodology (lcm-p). *J Psychiatr Res*. 1997;31(5):593-603.
84. Denicoff KD, Leverich GS, Nolen WA, et al. Validation of the prospective nimh-life-chart method (nimh-lcm-p) for longitudinal assessment of bipolar illness. *Psychol Med*. 2000;30(6):1391-1397.
85. Stone AA, Schwartz JE, Neale JM, et al. A comparison of coping assessed by ecological momentary assessment and retrospective recall. *JPSP*. 1998;74(6):1670-1680.
86. Robinson MD, Clore GL. Belief and feeling: Evidence for an accessibility model of emotional self-report. *Psychol Bull*. 2002;128(6):934-960.
87. Mansell W, Lam DH. A preliminary study of autobiographical memory in remitted bipolar and unipolar depression and the role of imagery in the specificity of memory. *Memory*. 2004;12(4):437-446.

88. Shimizu M, Kubota Y, Mason R, Baba H, Calabrese JR, Toichi M. Selective deficit of autobiographical incident memory in subjects with bipolar disorder. *Psychopathology*. 2009;42(5):318-324.
89. Kim WJ, Ha RY, Sun JY, et al. Autobiographical memory and its association with neuropsychological function in bipolar disorder. *Compr Psychiatry*. 2014;55(2):290-297.
90. Tohen M, Frank E, Bowden CL, et al. The international society for bipolar disorders (isbd) task force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009;11(5):453-473.
91. Hirschfeld RM, Calabrese JR, Frye MA, et al. Defining the clinical course of bipolar disorder: Response, remission, relapse, recurrence, and roughening. *Psychopharmacol Bull*. 2007;40(3):7-14.
92. Berk M, Post R, Ratheesh A, et al. Staging in bipolar disorder: From theoretical framework to clinical utility. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2017;16(3):236-244.
93. Bornstein RF. Toward a process-focused model of test score validity: Improving psychological assessment in science and practice. *Psychol Assess*. 2011;23(2):532-544.
94. Goodman LA, Corcoran C, Turner K, Yuan N, Green BL. Assessing traumatic event exposure: General issues and preliminary findings for the stressful life events screening questionnaire. *Journal of Traumatic Stress: Official Publication of The International Society for Traumatic Stress Studies*. 1998;11(3):521-542.
95. Ghaemi SN. Bipolar vs. Borderline - diagnosis is prognosis once again. *Acta Psychiatr Scand*. 2016;133(3):171-173.
96. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet*. 2016;387(10027):1561-1572.
97. Ghaemi SN, Bauer M, Cassidy F, et al. Diagnostic guidelines for bipolar disorder: A summary of the international society for bipolar disorders diagnostic guidelines task force report. *Bipolar Disord*. 2008;10(1 Pt 2):117-128.
98. Angst J, Gamma A, Bowden C, et al. Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with dsm-iv major depressive episodes. *Eur Arch Psychiatry Clin Neurosci*. 2012;262(1):3-11.
99. Association AP. *Diagnostic and statistical manual of mental disorders. Dsm-iv-tr*. 2000.
100. Berk M, Malhi GS, Cahill C, et al. The bipolar depression rating scale (bdrs): Its development, validation and utility. *Bipolar Disord*. 2007;9(6):571-579.
101. Guy W. Clinical global impressions scale. *ECDEU assessment manual for psychopharmacology*. 1976:217-222.

102. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the clinical global impressions (cgi) scale for use in bipolar illness (bp): The cgi-bp. *Psychiatry Res.* 1997;73(3):159-171.
103. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *The British journal of psychiatry.* 1979;134(4):382-389.
104. Hamilton M. A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry.* 1960;23(1):56.
105. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. *The British journal of psychiatry.* 1978;133(5):429-435.

ix. Tables

Table 1

Method	Benefits	Limitations	Published examples
Admission history/ Case records	<ul style="list-style-type: none"> Potential for increased reliability Doesn't rely on recall 	<ul style="list-style-type: none"> Admission doesn't equate to episodes Time-consuming to attain and use Privacy 	¹¹
Informants	<ul style="list-style-type: none"> May assist with recall Doesn't rely on (individuals' recall) 	<ul style="list-style-type: none"> Reliant on cooperation Differing reliability, dependant on individual Not standardised 	¹¹
Existing clinical tools/interview	<ul style="list-style-type: none"> Convenient, tools already being used for diagnosis (SCID, MINI) Structured Potential for standardisation 	<ul style="list-style-type: none"> Relies heavily on self-report, memory 	^{9,10,16,20}
Unprompted self-report	<ul style="list-style-type: none"> Brief 	<ul style="list-style-type: none"> Likely to be impacted by memory issues Likely to become less reliable with increasing NoE 	⁴²
Prompted self-report	<ul style="list-style-type: none"> Structured Well-designed prompts likely to aid recall (world or significant life 	<ul style="list-style-type: none"> Can be time consuming Currently not used consistently (e.g. different prompts) 	^{3,5,6,8,71,73,80}

Methods of Assessing Number of Episodes

	events, definition of episodes)		
Technology assisted recall	<ul style="list-style-type: none"> • Reliable • Doesn't rely on recall 	<ul style="list-style-type: none"> • Only useful prospectively 	92
Combination of methods	<ul style="list-style-type: none"> • Collates across multiple informants/sources 	<ul style="list-style-type: none"> • Unwieldy/feasibility • Time-consuming • Inconsistent across participants 	7,11,75

Table 2

Comparison of NoE Across Studies

Study	Inclusion criteria	Method of assessing NoE	Distribution
Bonnin, et al. ¹⁶	(1) 18 - 65 years old. (2) BD I according to DSM-IV criteria (3) Euthymic for at least 6 months	Clinical interview including SCID for DSM-IV-TR	<i>N</i> = 85 Grand mean NoE = 9.29 Grand mean dep = 3.99 Grand mean manic = 2.55 Grand mean mixed = .52
Martino, et al. ⁷²	(1) Age 18 – 60 (2) BD I or BD II (DSM-IV) (3) Euthymic for at least 8 weeks (4) 24-month follow-up available	SCID for DSM-IV-TR supported by clinical charts and direct patient interviews. When possible, attempts were made to verify these historical data with third-party reports (medical records, family interviews. Note that (hypo)manic episodes were defined as a period of at least one week with mild, moderate, or severe mania	<i>N</i> = 50 Mean NoE = 7.47 Mean dep = 4.16 (4.69) Mean hypo/manic = 3.31 (3.84)
Rosa, et al. ⁷⁵	(1) ≥ 18 years (2) Fulfillment of DSM-IV criteria for bipolar I or bipolar II disorder.	Episode definition/operationalisation not stated, SCID for DSM-IV-TR and examination of clinical records.	<i>N</i> = 131 Grand mean NoE = 16.69 Grand mean dep = 7.34 Grand mean manic = 3.97 Grand mean hypo = 4.56 Grand mean mixed = 0.86
Colom, et al. ³⁹ Colom, et al. ⁹³	(1) 18-65 (2) Diagnosis of bipolar disorder	Not explicitly specified – SCID for DSM-IV-TR was used to confirm diagnosis.	<i>N</i> = 120 Grand mean NoE = 9.56

	type I or II elicited by a trained psychiatrist (3) Euthymic for at least 6 months (4) Sufficient data on the prior course of illness		
Jimenez, et al. ⁷	(1) ≥ 18 years (2) Bipolar I or II DSM-IV-TR diagnosis, (3) Euthymic	Semistructured interview based on the SCID for DSM-IV-TR which also considered data from medical records, to gather sociodemographic and clinical information.	$N = 215$ Grand mean NoE = 12.94 Grand mean dep = 6.62 Grand mean manic = 3.06 Grand mean hypo = 2.53 Grand mean mixed = .73
Martínez- Arán, et al. ¹⁷	(1) DSM-IV Bipolar I or II (2) Euthymic, manic or experiencing MDE according to DSM-IV criteria (age criterion not specified, adult)	SCID plus additional clinician/informant information as available	$N = 108$ Grand mean NoE = 14.74 Grand mean dep = 7.35 Grand mean manic = 3.26 Grand mean hypo = 2.98 Grand mean mixed = .87
MacQueen, et al. ¹¹	(1) 18-65 (2) Bipolar I (DSM- III-R) (3) Euthymic and non-rapid cycling	SCID for DSM-III-R; medical chart records, further patient interviews, family members, treating clinicians and life charts, where available, were also consulted to determine the most accurate estimate of past number of episodes.	$N = 64$ Mean, NoE = 8.8 Mean dep = 5.2 Mean manic = 3.6
Mansell, et al. ⁸⁵	(1) BD I (DSM-IV) (2) In remission (age criterion not specified, adult)	Not explicitly disclosed, SCID used for diagnosis	$N = 19$ Mean NoE = 9 Mean dep = 6 Mean manic = 3
Bourne, et al. ¹⁸	Individual patient data meta-analysis including: (1) 18-65 (2) Bipolar Disorder (not-defined)	Where possible, demographic and clinical variables were also collected for each primary data set including number of prior manic and depressed episodes.	Mean dep ($n = 992$) = 5.6 (10.7) Mean manic ($n = 989$) = 3.4 (4.5)

	(3) Euthymic		
Soni, et al. ¹⁰	(1) 18-55 (2) Bipolar disorder according to ICD-10 (3) Euthymic	Number of episodes was gathered during clinical interview including MINI	<i>N</i> = 61 Grand mean NoE = 7.42 Grand mean dep = 3.53 Grand mean manic = 3.89
Scott, et al. ³⁸	(1) ≥ 18 (2) DSM-IV diagnosis of bipolar disorder I or II (3) history of two or more episodes one of which must have been within 12 months of recruitment; and (4) in contact with mental health services within the past 6 months.	Data collected before randomisation included diagnosis according to SCID (DSM-IV) and “diagnoses of past episodes of bipolar disorder according to DSM-IV criteria”.	<i>N</i> =253 <i>Categorical data only</i> Number of previous episodes, n (%) 2-6: 74 (29%) 7-11: 54 (21%) 12-29: 59 (23%) ≥ 30: 66 (26%) Depressive episodes: median (IQR): TAU: 5 (2-15) CBT: 6 (3-20) Hypomanic/manic/mixed episodes: median (IQR): TAU: 4 (2-9) CBT: 4 (2-8)
Peters, et al. ⁸	Full step BD sample: (1) ≥ 18 STEP-BD (2) Individuals seeking outpatient treatment (3) Meeting DSM-IV diagnostic criteria for bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified (NOS), cyclothymia or schizoaffective disorder, bipolar type	Affective Disorders Evaluation (ADE) (Sachs et al., 2002) provided Information regarding number of previous episodes.	<i>Full STEP-BD sample (N= 4361)</i> Depressive episodes: 1-9: 1369 (39%) 10-20: 642(18%) ≥ 20: 1480 (42%) (Hypo)manic episodes: 1-9: 1572(45%) 10-20: 604 (17%) ≥ 20: 1312(37%) (n and % of valid cases, no total episodes reported) <i>RCT for bipolar depression subsample (N=205)</i> Depressive episodes: 1-9: 68 (33%) 10-20: 29(14%)

	Subsample, RCT for bipolar depression: (1) ≥ 18 (2) DSM-IV criteria for bipolar I or II disorder (3) Current acute episode of depression (4) Be taking or willing to initiate treatment with a mood-stabilizing or atypical antipsychotic medication and willing to undergo psychotherapy		≥ 20 : 108 (53%) (Hypo)manic episodes: 1-9: 75 (37%) 10-20: 33 (16%) ≥ 20 : 97 (47%)
Swann, et al. ³⁰ Swann, et al. ³² Bowden, et al. ⁹⁴	(1) 18-65 (2) Meet RDC criteria for manic disorder (3) Currently manic	The Schedule for Affective Disorders and Schizophrenia (SADS) and Research Diagnostic Criteria (RDC) were used to make diagnoses. Course of illness was examined in detail by using all available sources of information including medical records and collateral interviews where available.	$N = 179$ Manic (n = 157): range 1-52, mode 8 Depressive (n= 130): range 1-36, mode 2
Magalhaes, et al. ⁶ STEP-BD	STEP-BD standard care pathways participants with sufficient data: (1) Aged ≥ 15 (2) Meeting DSM-IV diagnostic criteria for bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified (NOS),	Affective Disorders Evaluation (ADE)	$N = 3345$ < 5: 344 (10.3%) 5-10: 1275 (38.1%) ≥ 10 : 1726 (51.6%)

	cyclothymia or schizoaffective disorder, bipolar type (3) Seeking outpatient treatment		
Berk, et al. ²⁹	Meta-analysis, twelve bipolar disorder studies with a total of 4,346 participants (mania, depression, and maintenance trials.)	Varied per study	(1-5, 5-10, ≥ 10), with 55% of participants with episode data reporting ≥ 10 episodes.

Table 3

Suggested Definitions for Mood Episodes

Construct	Definition	Potential operationalisation
Manic Episode	DSM-5 criteria ⁷⁶ . If ICD-10 criteria are used, this should be noted.	As per DSM-5 criteria, see Appendices for assessment questions.
Major Depressive Episode	DSM-5 criteria ⁷⁶ . If ICD-10 criteria are used, this should be noted.	As per DSM-5 criteria, see Appendices for assessment questions.
Hypomanic Episode	DSM-5 criteria ⁷⁶ . If ICD-10 criteria are used, this should be noted (in particular, duration criteria: see Hypomanic Episode, short duration below).	As per DSM-5 criteria, see Appendices for assessment questions.
Hypomanic	The validity of the 4-day minimum duration of	Full DSM-5 criteria for a

Episode, short duration	<p>symptoms for a hypomanic episode within the DSM-5 has been questioned^{95,96}. Several authors have suggested that this does not reflect phenomenology and recommended a reduced duration of 2 to 3 days^{95,97,98}.</p> <p>Should shorter duration episodes of 2 to 3 days be included, these should be recorded as a separate type and authors should consider excluding from aggregates.</p>	hypomanic episode, with a reduced duration criteria of ≥ 2 days.
Mixed Features (previously Mixed Episode)	<p>DSM-5 criteria⁷⁶. If DSM-IV⁹⁹ criteria are used (and therefore 'Mixed episodes' are recorded as a separate category), authors should note this and include these within total NoE and number of manic episodes when aggregating.</p>	
Remission	<p>The absence or minimal symptoms of both mania and depression for at least 1 week (at least eight weeks for 'sustained remission').⁹¹</p> <p><i>Depression:</i> Any present symptoms should not include DSM threshold sad mood or loss of pleasure (Criteria A1, A2)⁹⁰.</p> <p><i>Mania:</i> Any present symptoms should be mild, in particular criterion A. May therefore meet criteria for hypomania.</p>	<p>Consider rating each symptom on a severity scale such as the CGI (1-7).</p> <p><i>Depression:</i> Fewer than 3 of the 7 remaining DSM A criteria, and those present rated $\leq 3$⁹⁰.</p> <p><i>Mania:</i> DSM A criterion for mania < 2, any B criteria rated ≤ 3 and no two B criteria rated = 3⁹⁰.</p> <p>Rating scales: YMRS ≤ 8 MADRS ≤ 10 or HAMD ≤ 7 CGI-BP-S $\leq 2$⁹¹ BDRS $\leq 8$⁹⁰.</p>
Relapse	<p>The return of symptoms satisfying the full syndrome</p> <p>criteria for an episode that occurs during the</p>	<p>Symptoms meeting DSM episode criteria, following at least 1, but less than 8 weeks of</p>

	period of remission ⁹¹ .	remission.
Recurrence	Occurrence of a new syndromal episode meeting DSM criteria ⁹¹ , during a period of sustained remission.	Symptoms meeting DSM episode criteria, following at least 8 weeks of remission.

Note: BDRS = Bipolar Depression Rating Scale ¹⁰⁰, CGI = Clinical Global Impression ¹⁰¹, CGI-I-BP = CGI-Improvement scale for bipolar disorder ¹⁰², MADRS = Montgomery-Asberg Depression Rating Scale ¹⁰³, HAM-D = Hamilton Rating Scale for Depression ¹⁰⁴, YMRS = Young Mania Rating Scale ¹⁰⁵.

xi. Appendix

Appendix A

Current Structured Tools Employed to Assess Number of Episodes

Measure	Specific NoE question/s	Prompt type, example	Comments
Mini International Neuropsychiatric Interview ¹ , version 7.0.2	How many episodes of depression did you have in your lifetime? Did you have 2 more of these (manic) episodes lasting 7 days or more in your lifetime? Did you have 2 more of these (hypomanic) episodes lasting 4 days or more in your lifetime?	Context of definition and assessment of episode	Manic/hypomanic NoE not asked by default (only asks whether more than once)
Structured Clinical Interview for the DSM-5 ²	How many separate times in your life have you been (depressed/OWN WORDS) nearly every day for at least 2 weeks and had several of the symptoms that you described, like (SXS OF CURRENT MDE)?	Context of definition and assessment of episode	Manic/ hypomanic not asked by default, asked about age at onset instead
Affective Disorders Evaluation ³	The time we've been talking about is what we would call (hypo)mania. Using that time as a guide, how many times have you been like that for as long as 1 wk? The time we've been talking about is what we'd call an episode of depression. Using that time as a guide, how many times have	Context of definition and assessment of episode	Response options are categorical (0, 1, 2, 3-4 5-9 10-20 20-50) ADE is no longer available online

	you been like that for as long as 2 weeks?		
NIMH Life Chart (retrospective) ⁴	The time line in the middle of the chart (marking the months and years) is also called the baseline indicating a level or balanced mood state, i.e., you are not depressed or hypomanic or manic. Episodes of depression are drawn below the baseline (which is also the date line) and episodes of mania are drawn above the baseline	Prompts include list of major life events, medications changes, episode severity	Instructs users to ask friends and family about number of episodes

References

1. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33;quiz 34-57.
2. First MB. Structured clinical interview for the DSM(SCID). In: *The Encyclopedia of Clinical Psychology*. John Wiley & Sons, Inc.; 2014.
3. Sachs GS, Guille C, McMurich SL. A clinical monitoring form for mood disorders. *Bipolar Disord*. 2002;4(5):323-327.
4. Leverich GS, Post RM. Life charting of affective disorders. *CNS spectrums*. 1998;3(5):21-37.

Appendix B

Examples of Questions to Assess Episodes of Different Types

Episode type	Definition	Question	Prompts and probes
Major Depressive Episode	<p>“An episode of depression involves symptoms like:</p> <ul style="list-style-type: none"> • sadness • less interest or pleasure in things you normally enjoy • low energy • changes to your sleep, appetite or concentration • feelings of hopelessness • thoughts of suicide <p>To be considered an 'episode' of depression, several of these symptoms need to have been present for most of</p>	<p>“How many episodes of depression have you experienced in your lifetime?”</p>	<p>“It may help you to start by remembering your first episode of depression. What age were you when you first experienced an episode of depression?”</p> <p>“Some people notice a pattern in their episodes, for example experiencing depression over the colder months followed by an elevated episode. Have you noticed any patterns in your own experience?”</p> <p>“What are some significant life events you’ve experienced (such as beginning or finishing</p>

<p>Author Manuscript</p>	<p>the day, nearly every day for at least two weeks and you'd feel or behave noticeably different to how you normally would. These episodes of depression may have occurred before or after you were diagnosed with bipolar disorder.”</p>		<p>university, changing jobs, marriages, having children, moving home, or experiencing a loss)? Do you recall any episodes of depression around these times?”</p> <p>“On average, how many episodes of depression do you experience per year?” Has this always been around this often, or more or less frequently in the past?”</p> <p>“You talked about a period of depression which required you to spend some time in hospital, I’m wondering if there have been other episodes of depression that didn’t require hospitalisation, but that were still significant?”</p> <p>“We know that thinking about difficult times in your past can sometimes be upsetting. While we’re talking about your past experiences, if you notice that this is the case for you, can you please let me know or ask to pause our discussion?”</p>
<p>Manic</p>	<p>“Elevated episodes involve elevated mood (feeling</p>	<p>“How many episodes</p>	<p>“It may help you to start by remembering</p>

<p>Episode</p> <p>Author Manuscript</p>	<p>high, elated, or very irritable), including symptoms like:</p> <ul style="list-style-type: none"> • having more energy or less need for sleep • being more talkative or active • racing thoughts • making lots of plans or goals • increased self-esteem • pleasurable behaviours with negative consequences, like spending a lot of money <p>To be considered a 'manic episode', several of these symptoms will have occurred for at least a week and caused problems in areas like work, relationships, or friendships, or resulted in you being hospitalised.</p> <p>These episodes of mania may have occurred before or after you were diagnosed with bipolar disorder.”</p>	<p>of mania have you experienced in your lifetime?”</p>	<p>your first episode of mania. What age were you when you first experienced an episode of mania?”</p> <p>“What are some significant life events you’ve experienced (such as beginning or finishing university, changing jobs, marriages, having children, moving home, or experiencing a loss)? Do you recall any episodes of mania around these times?”</p> <p>“On average, how many episodes of mania do you experience per year?” Has this always been around this often, or more or less frequently in the past?”</p> <p>“You talked about an elevated period which required you to spend some time in hospital, I’m wondering if there have been other times that didn’t require hospitalisation, but involved elevated moods which impacted your functioning?”</p> <p>“We know that thinking about difficult times in your past can sometimes be upsetting.</p>
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			While we're talking about your past experiences, if you notice that this is the case for you, can you please let me know or ask to pause our discussion?"
Hypomaniac Episode	<p>"Hypomania is similar to mania, except that the symptoms are usually less severe and don't affect your functioning, but would be noticeable to someone who knows you. For example, you might have:</p> <ul style="list-style-type: none"> • Needed less sleep • Been more talkative • Noticed your thoughts racing • Become more distractible • Made lots of plans or goals • Engaged in more pleasurable activities, even if these were risky <p>'Hypomaniac episodes' last four days or more. These episodes of hypomania may have occurred before or after you were diagnosed with bipolar disorder."</p>	<p>"How many episodes of hypomania that lasted at least four days have you experienced in your lifetime? "</p>	<p>"It may help you to start by remembering your first episode of hypomania. What age were you when you first experienced an episode of hypomania?"</p> <p>"What are some significant life events you've experienced (such as beginning or finishing university, changing jobs, marriages, having children, moving home, or experiencing a loss)? Do you recall any episodes of hypomania around these times?"</p> <p>"On average, how many episodes of hypomania do you experience per year?" Has this always been around this often, or more or less frequently in the past?"</p> <p>"We know that thinking about difficult times in your past can sometimes be upsetting. While we're talking about your past</p>

			experiences, if you notice that this is the case for you, can you please let me know or ask to pause our discussion?"
Mixed Episode or Mixed features*	<p>Assessment based on whether DSM-IV-TR or DSM-5 criteria is used.</p> <p>DSM-IV-TR: "Mixed episodes involve these elevated symptoms at the same time as symptoms of depression for at least a week. These mixed episodes may have occurred before or after you were diagnosed with bipolar disorder."</p> <p>DSM-5: "Mixed features means that, during any of the episodes of mania, hypomania or depression you've experienced, you also experienced some symptoms of the other type of episode at the same time".</p>	<p>"How many episodes have you experienced in your lifetime which included some elevated and some depressed symptoms? Did you include any of these in the previous questions? "</p>	

*Mixed episodes were replaced in the DSM-5 by a mixed features specifier, applied to Manic, Hypomanic or Major Depressive Episodes. The key difference is that full criteria for episodes of both types were required to be classified as a Mixed Episode (DSM-IV-TR), while a mixed features specifier is applied when full criteria are met for any type of episode, plus three or more criteria of an episode of another type (DSM-5). Therefore, these episodes would not appear as a separate 'Mixed Episode' but would be categorised and 'counted' under the relevant threshold episode (manic if full criteria for both are met).

Figure 1. NoE construct.

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Figure 2. Summary of cognate clinical course factors with NoE

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