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Correlates, Course, and Outcomes of Increased Energy in Youth with Bipolar Disorder Contributors

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Abstract

Objectives: Compare longitudinal trajectories of youth with Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Bipolar Disorder (BD), grouped at baseline by presence/absence of increased energy during their worst lifetime mood episode (required for DSM-5).

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Methods: Participants from the parent Course and Outcome of Bipolar Youth study (N = 446) were assessed utilizing The Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS), KSADS Mania Rating Scale (KMRS), and KSADS Depression Rating Scale (KDRS). Youth were grouped at baseline into those with increased energy (meeting DSM-5 Criteria A for mania) vs. without increased energy (meeting DSM-IV, but not DSM 5, Criteria A for mania), for those who had worst lifetime mood episode recorded (n = 430). Youth with available longitudinal data had the presence/absence of increased energy measured, as well as psychiatric symptomatology/clinical outcomes (evaluated via the Adolescent Longitudinal Interval Follow-Up Evaluation), at each follow-up for 12.5 years (n = 398).

Results: At baseline, the increased energy group (based on endorsed increased energy during worst lifetime mood episode; 86% of participants) vs. the without increased energy group, were more likely to meet criteria for BD-I and BD Not Otherwise Specified, had higher KMRS/KDRS total scores, and displayed poorer family/global psychosocial functioning. However, frequency of increased energy between groups was comparable after 5 years, and no significant group differences were found on clinical/psychosocial functioning outcomes after 12.5 years.

Limitations: Secondary data limited study design; groupings were based on one time point.

Conclusions: Results indicate no clinically relevant longitudinal group differences.

Keywords

increased energy; bipolar disorder; longitudinal studies; child and adolescent psychiatry

1. Introduction

The conceptualization of bipolar disorder (BD) has recently changed, such that in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Association, 2013), diagnosing bipolar spectrum disorders now requires the presence of increased energy as a gate A Criterion for hypo/mania. This change has resulted in some conflicting reactions in the field. Some researchers suggest requiring increased energy in addition to the other gate criteria improves the diagnostic clarity of hypo/mania (Akiskal et al., 2001; Benazzi and Akiskal, 2003), while others suggest this requirement is too restrictive, and endorsement of any of the three gate criteria should be sufficient (Angst et al., 2012; Angst, 2013; Machado-Vieira et al., 2017).

Previous research has explored the factor structure of the criteria for mania, and found that increased energy has the highest factor loading on mania severity in adults with BD. Results suggest increased energy is the core symptom of mania, and should be more highly considered than changes in mood when diagnosing mania in adults (Cheniaux et al., 2014). Other research on adults with BD suggests a two-factor model of mania that consists of increased energy (“energized-activity”) and “irritability-racing thoughts”, revealing elated mood did not have a major loading on either component (Benazzi and Akiskal, 2003). A recent machine learning study in adults with BD suggests increased (evening) energy might be a better predictor than mood or sleep ratings for forecasting manic and depressive episodes (Ortiz et al., 2018). Similar results have been found when examining correlations between self-reported symptoms of mania and clinician-rated mania severity, showing self-

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reported increased energy and activation, not mood state, was the only subscale examined that contributed significantly to the prediction of clinician-rated mania (Bauer et al., 1991).

Cross-cultural studies of mania criteria among adults with BD also support the addition of increased energy to Criteria A in DSM 5 (Akiskal, 2003; Akiskal et al., 2001; Angst et al., 2012). Furthermore, a recent meta-analysis of studies of adults with BD supports increased energy in Criteria A for hypo/mania. However, the authors caution there are many limitations in the available data (e.g. “few high-quality studies, mean activity levels were low in participants with BD, compared to participants with other disorders or healthy controls; activation in mania may be better characterized by its variability, predictability, or complexity, rather than mean levels”), and further methodologically sound research is necessary (Scott et al., 2017).

Little research exists on the increased energy criterion in youth with BD. This is despite results of a recent meta-analysis of the clinical characteristics of pediatric hypo/mania that found the most frequent manic symptom among all studies of youth with BD was increased energy (79%), compared to euphoric/elated mood (64%) (Van Meter et al., 2016). Of the limited information available, research shows increased energy is a potentially important prodromal characteristic in youth, finding it was significantly more common in individuals who later experienced mania with psychotic symptoms (Correll et al., 2007). One study from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), which includes older adolescents as well as adults, examined the impact of requiring the increased energy A Criterion (Machado-Vieira et al., 2017). Point prevalence data to show the changes in diagnostic criteria from DSM-IV to DSM-5 revealed a reduction in the prevalence of hypo/mania in individuals 15 years and older with BD (8.3% based on DSM-IV criteria, reduced to 4.3% based on DSM 5 criteria). However, there were no differences in psychosocial functioning or clinical outcomes between those with or without increased energy after one year of follow-up (i.e., no between-group differences in Global Assessment of Functioning Clinical Global Impressions scale) (Machado-Vieira et al., 2017).

The current study aims to build upon the findings from the STEP-BD investigation by focusing on a youth sample, as well as expanding the clinical outcomes and length of follow-up examined. Using data from the Course and Outcome of Bipolar Youth (COBY) study provides an opportunity to further explore the potential clinical impact of the DSM 5 diagnostic changes to hypo/mania criteria in youth with BD. The current study uses secondary analyses to examine potential differences in participants who met full DSM-5 Criteria A for hypo/mania, including increased energy, during their worst lifetime mood episode (IE+), compared to participants who did not endorse the increased energy criterion and therefore met DSM-IV, but not DSM 5, Criteria A for hypo/mania during their worst lifetime mood episode (IE-). This is primarily a paper of phenomenology, looking at the trajectory of increased energy in youth meeting DSM 5 versus DSM-IV hypo/mania criteria over the course of 12.5-year follow up, and investigating if there are any significant differences in clinical outcomes over time between IE+ and IE− youth. Based on the limited outcome data available in the field comparing youth who met criteria for DSM-IV versus DSM 5 BD (Machado-Vieira et al., 2017), it was hypothesized that there would be no

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significant differences between the IE+ and IE− youth on clinical or psychosocial functioning outcomes over the 12.5 year follow up.

2. Method

2.1 Participants

Participants were recruited for the COBY study previously described elsewhere (Axelson et al., 2006; Birmaher and Axelson, 2006; Hunt et al., 2009). In brief, youth aged 7 to 17 years (mean [SD] age, 13 [3] years) were recruited from 2000 to 2006 at three study sites (University of Pittsburgh Medical School [UPMC], Brown University, and University of California Los Angeles [UCLA]). All youth met either DSM-IV criteria for BDI, BDII, or COBY operationally defined BD not otherwise specified (NOS). BD-NOS was defined as distinct period(s) of expansive, elevated, or irritable mood plus (1) at least two DSM-IV manic symptoms (three if the mood is irritable only) associated with the onset of abnormal mood; (2) change in functioning with the onset of these affective symptoms; (3) presence of abnormal mood and manic symptoms for a minimum of 4 hours a day (not necessarily consecutive); and (4) lifetime duration of a minimum of four days (not necessarily consecutive). Participants with current or lifetime diagnoses of schizophrenia, mental retardation, autism, and mood disorders secondary to substance abuse, medical conditions, or use of medications, were excluded. Recruitment was completed from consecutive admissions to outpatient clinics (65%), and inpatient units (16%), utilizing advertisements (11%), and professional referrals (8%), and were enrolled independent of current BD state or treatment status.

The current study explores secondary analyses of the parent COBY study (N = 446) in a subsample of 430 participants diagnosed with BDI, BDII, and BDNOS for baseline analyses; 16 participants who were enrolled early in the study did not have a most serious past episode of mania recorded, and therefore these participants were not included in any of these analyses. Over follow-up, 398 participants had available data for analyses of follow-up data. This subsample was interviewed on average every 8.7 months (SD = 5.2) for a total of 12.5 years. Approximately half were male (52%), with an average age of 13 years (SD=3). 81% of participants were self-reported White, and 6% were self-reported Hispanic. No significant differences were observed between the 398 participants who participated at baseline, and the 32 participants who did not participate at follow-up.

2.2 Procedure

Approval was obtained from each study site’s Institutional Review Board (IRB). Informed consent was obtained from primary caregiver(s), and assent was obtained from youth prior to participation. All assessments were completed by research staff with extensive clinical research experience, who were trained to administer the instruments with a high level of reliability within and between the sites. The interviewers reviewed the participants’ symptomatic and psychosocial course with a study investigator, who was ultimately responsible for clinical ratings. Participants’ medical records were also reviewed when necessary. Interviewers were not blind to participants’ prior diagnoses.

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2.2.1 Measures—We examined several variables, including mood symptom history, age of BD onset, history of other psychiatric diagnoses and co-morbid symptomatology (particularly Attention Deficit Hyperactivity Disorder [ADHD] and anxiety), family functioning and conflict, and history of suicidality, because they have been identified as having significant effects on the course and trajectory of mood symptoms in our COBY sample (Birmaher et al., 2014).

Non-Mood and Mood Disorder Assessments: Semi-structured interviews were conducted with youth and a primary caregiver. Psychiatric disorders, suicidal ideation (SI), suicidal acts (SA), and non-suicidal self-injury (NSSI) were assessed at baseline using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-PL; (Kaufman et al., 1997)). Mood symptom severity was measured using the KSADS Depression Rating Scale (KDRS (Kaufman et al., 1997); item score range 0–6, total score range 0–61) and KSADS Mania Rating Scale (KMRS (item score range 0–6, total score range 0–63), derived from their respective sections in the KSADS-PL (Chambers et al., 1985). Suicide-related items (SI, SA, and NSSI) were also assessed over the course of follow-up using the KDRS. As indicated in the instructions for the KDRS and KMRS, the items are meant to determine symptom severity during a period of time prescribed by the study (usually a 1-week period); the COBY study investigators chose to focus on the most severe lifetime week (baseline), and the most severe week in the month prior to the assessment (baseline and all follow-ups). The overall KSADS kappas for psychiatric disorders were ≥0.8 (Birmaher et al., 2014). The Intraclass Correlation Coefficients (ICC) for the KMRS and KDRS interrater reliability were 0.95 or more, and internal consistency Cronbach's alpha were ≥0.94, determined prospectively with 22 participants from a BD outpatient clinic (Axelson et al., 2003)

Symptomatology and Service Utilization Assessments: Psychiatric symptomatology and intensive service utilization (days of inpatient hospitalization) were assessed over follow up using the Psychiatric Status Rating (PSR) scales (Warshaw et al., 2001) from the Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE; (Keller et al., 1987)). The PSR scales were developed to generate analyzable data about the course of the participant's psychopathology. The PSR uses numeric values that have been operationally linked to DSM-IV criteria, which is gathered in the interview and then translated into ratings. Scores on the PSR scales range from 1 (no symptoms) to 2–4 (increasing sub-threshold symptoms and impairment) to 5–6 (full criteria with increasing degrees of severity or impairment). Having a PSR of 1 or 2 for 8 consecutive weeks constitutes a recovery from the episode. Participants were considered to have a recurrence (new episode) if they had a PSR score of 5 or 6 with a duration of 1 week for mania/hypomania, or 2 weeks for depression (Birmaher et al., 2006; Judd et al., 2002).

To obtain data for the PSR ratings, the interviewer reviews the participant's symptoms reported at the last interview, and then probes for changes in symptomatology forward in time to the current interview date. These "change points" are later translated by the interviewer into PSR ratings (indicating the severity level of an episode, as well as whether the participant has recovered or relapsed) for each week of the follow-up period. Thus, the

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interviewer rates each week at the same PSR number until there is a “change point” identified, then rates all subsequent weeks at this PSR number until there is another “change point” identified. As previously reported, the reliability of the PSR in COBY is good/very good (Axelson et al., 2011). The PSR reliability of percentage of time meeting full DSM-IV diagnostic threshold for a mood episode yielded an Intraclass Correlation (ICC) = 0.85. The ICC for percentage of time without significant mood symptoms was 0.82. Reliability for PSR mood disorder ratings over the course of COBY was an average Kendall’s W of 0.8.

Additional Anxiety and Functional Assessments: Additional measurement of anxiety disorders was assessed using the Screen for Child Anxiety Related Disorders (SCARED) (Birmaher et al., 1999). Global functioning was assessed using the Children’s Global Assessment Scale (CGAS; (Shaffer et al., 1983)) and the Global Assessment of Functioning Scale (GAF; (Endicott et al., 1976)), depending on age at evaluation (CGAS = 7–21 years, GAF = 22+ years). Family functioning was assessed using the Behavioral Control Scale (BCS) (Kolko, 2007).

2.2.2. Participant Groupings—Participants were separated into two groups, those “with increased energy” (IE+) who met full DSM 5 A Criteria during their most severe lifetime mood episode identified at study baseline (n = 368), and those “without increased energy” (IE-) who met DSM-IV, but not DSM 5, A Criteria during the most severe lifetime mood episode identified at study baseline (n = 62). Participants in the IE+ group had a clinically elevated score (≥3 based upon the previously derived clinically significant individual score cut-off (Axelson et al., 2003)) on the KMRS elation item and/or irritability item, as well as on the increased energy item, during their most severe lifetime mood episode. Youth in the IE− group scored in the clinically elevated range on the KMRS elation item and/or irritability item, but did not have elevated increased energy during their most severe lifetime mood episode. Individual KMRS Criterion B items were evaluated to determine if the IE+ group presented with additional elevated mania symptom scores compared to the IE− group. This was intended to add to the diagnostic and clinical picture of the two baseline energy groups, as well as to be consistent with similar prior COBY studies (Hunt et al., 2009; Hunt et al., 2013).

2.2.3. 2.2.3 Statistical analyses—Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 22, Stata (Stata Corp, College Station, TX; version 16) and Mplus (Muthen & Muthen, Los Angeles, CA, version 8).

Baseline Analyses: Most severe lifetime energy group differences on demographics, psychopathology, illness course, and suicidality were examined at baseline using x^2 statistics for categorical variables. A series of Analyses of Covariance (ANCOVAs) controlling for age, sex, and lifetime diagnosis of ADHD, were used for continuous variables at baseline. Effect size was calculated by Hedge’s *g*, which is a standardized mean difference effect size statistic interpretable as a Cohen’s d (.2 small, .5 medium, .8 large) (Hedges, 1981). These analyses used two-tailed tests of statistical significance ($\alpha = .05$) as a guide to inference.

Analyses of outcomes observed over follow-up: Mixed effect generalized linear modeling was used to assess the stability of increased energy in each group over 12.5 years, using the

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scores on the KMRS that were administered at each follow-up (worst week of the month prior to each follow-up). Generalized linear modeling was also used to evaluate models for the prospectively collected PSR data on depression and mania, and global psychosocial functioning, based on C-GAS and GAF scales. We specifically used a mixed effect ordinal logistic regression model to examine the cumulative risk of SI, SA, NSSI, and any suicidality (either SI, SA, or NSSI) occurring ever during the follow-up period, based on KDRS scores (worst week of the month prior to each follow-up). This data was then dichotomously coded into either occurring or not occurring over the course of follow up. The "cumulative risk" is the measure of incidents of these suicide-related outcomes over time throughout the 12.5-year follow-up period. Lastly, Poisson regressions were used to analyze PSR group differences in number of psychiatric hospitalizations, and percentage of time spent in depression, mania, hypomania, and any mood episodes, throughout the 12.5-year follow-up.

3. Results

3.1 Baseline Demographic/Clinical Characteristics of the Two Energy Groups

At baseline, the IE+ group represented 86% (368/430) of the sample, and the IE− group represented 14% (62/430) of the sample. We found significant differences between the two energy groups at baseline by BD category (x^2 = 12.18, p = .002). Specifically, the IE+ participants were more likely to meet criteria for BDI and BDNOS, compared to the IE− group. There were no group differences on rates of BDII diagnosis. No significant differences were found between the energy groups for all other categorical baseline analyses, including demographic variables (p = .12 - p = .56), whether or not participants were currently on any psychotropic medication (x^2 = .90, p = .34), other comorbid psychiatric diagnoses (p = .10 - p = .95), psychiatric hospitalization (x^2 = .47, p = .49), illness course (x^2 = 1.16, p = .76), SI (x^2 = 1.98, p = .16), SA (x^2 = .14, p = .71), and NSSI (x^2 = 2.50, p = .11).

ANCOVA analyses using age, sex, and lifetime ADHD diagnosis as covariates (see Table 1) showed significantly higher mean scores in the IE+ group compared to the IE− group at baseline on baseline mania total score, as well as mania and depression total scores, during the most severe lifetime episode. The IE+ group also had higher mean scores on several Criteria B symptoms of hypo/mania compared to the IE− group at baseline. Lastly, the IE+ group had poorer family functioning, and poorer overall psychosocial functioning, at baseline compared to the IE− group.

3.2 Follow-up Outcomes of the Two Increased Energy Groups

Results of mixed effect generalized linear modeling examining the stability of the KMRS increased energy criterion over the 12.5 year follow up showed a comparable level of energy between the two groups by year 5 (see Figure 1). The convergence occurred as the IE+ group experienced a decline in energy over time. Examining the entire 12.5 years of follow-up for all outcomes, generalized linear modeling (see Table 2) indicated no significant between group differences on PSR scores for depression or mania, or global psychosocial functioning, over the course of follow-up (on average, and at last follow-up). The mixed

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effect ordinal logistic regression model revealed no significant group differences over follow-up on PSR scores for SI, SA, NSSI, or any suicidality (either SI, SA, or NSSI), over the course of follow-up (cumulatively through the last follow-up). Lastly, Poisson regressions found no group differences in PSR number of psychiatric hospitalizations, time spent in a depressive episode, time in a manic episode, time in a hypomanic episode, or time spent in any mood episode, over the course of follow-up (on average, and at last follow-up).

4. Discussion

The current study used secondary analyses from the COBY parent study to evaluate increased energy, the A Criterion required for hypo/mania diagnosis in DSM 5, in a subsample of youth with DSM-IV diagnosed BD. Initial hypotheses stated there would be no significant differences on clinical or psychosocial functioning outcomes over the 12.5 year follow-up between youth who met full DSM-5 criteria for hypo/mania, including endorsement of increased energy during their worst lifetime mood episode (IE+), compared to youth who met DSM-IV, but not DSM 5 hypo/mania, due to a lack of increased energy during their worst lifetime mood episode (IE-). Findings of the current study show: 1) significant group differences were found between the IE+ and IE− groups at baseline on mood symptoms, family functioning, and global psychosocial functioning; 2) the distinction in energy level between groups was eliminated within five years, and remained indistinguishable for the remainder of follow up, as the degree of energy in the IE+ group lessened over time; and 3) there were no post-baseline significant group differences on clinical or psychosocial functioning outcomes over 12.5 years of follow-up. It is interesting to note the presence of baseline group differences, showing greater mania symptom severity, poorer family functioning, and poorer global psychosocial functioning in the IE+ group, even though no group differences were found over the course of follow up. Future research that does not rely on secondary analyses may be able to identify additional factors to help explain why group differences exist at baseline but are no longer apparent at follow up.

In summary, the results of the current study indicate that participants in the IE− group who met DSM-IV criteria for hypo/mania, but did not meet criteria in DSM-5 due to the change in the increased energy criterion, show no clinically relevant differences over 12.5 years, compared to participants in the IE+ group who did meet DSM-5 criteria. These results align with those of the STEP-BD study, which showed that the changes in diagnostic criteria from DSM-IV to DSM-5 reduced the prevalence of hypo/mania, though there were no changes in longitudinal outcomes (Machado-Vieira et al., 2017). The current study extends these findings to youth with BD. Historically, a large emphasis has been placed on differences between BD in adults and BD in youth. However, a recent review by many experts in the field of BD suggest this emphasis on developmental differences may be overstated (Goldstein et al., 2017). The similarities in results of the STEP-BD study, which was primarily with adults, and the current COBY study in youth, supports the notion that there may be more commonalities along the developmental spectrum of BD than previously thought.

The longitudinal examination of the trajectory of increased energy by group is unique to the current investigation. The convergence between groups within five years in energy levels

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occurred as the IE+ group experienced a decline in energy over time. Perhaps this decline in increased energy is a byproduct of normal development, as youth have been shown to naturally display less energy as they age. This pattern of decreased energy over time has also been shown in those with other psychiatric disorders (besides BD), as they transition from childhood to adulthood. Specifically, research on ADHD has found that the symptom of hyperactivity appears to decline over the course of development from childhood through adulthood (Martel et al., 2012). Of note, research shows youth with BD (compared to adults with BD) are more likely to experience episodes of elated mood/increased energy, as indicated in both community and clinical samples (Geller et al., 2008; Lewinsohn et al., 1995), while adults with BD (compared to youth with BD) are more likely to experience depressive episodes over the course of illness (Collaborative Depression Study (CDS)) (Coryell et al., 1998; Judd et al., 2002). Thus, it seems that the overall progression with age, regardless of diagnosis, is towards a state of less energy.

Overall, the results of the current study suggest that some clinically relevant differences may exist between youth who do versus do not endorse increased energy at a given time point, even though these differences do not appear to persist over time. Of clinical importance, while the addition of increased energy as a necessary criterion for mania may reduce false positive diagnosis of youth with BD, this additional A Criterion may result in lack of BD diagnosis for some youth who met criteria for BD under DSM-IV. It would be prudent for clinicians to continue to think of endorsement of any A Criterion as important clinical information to consider when conceptualizing and monitoring mood symptoms and psychosocial functioning, with or without increased energy.

Outcomes of the current investigation provide research questions for future studies related to the clinical utility of the increased energy criterion. Clinical validation strategies introduced by Kendell (Kendell, 1989) outline the empirical evidence base for supporting arguments for the validity of newly developed nosological categories. They also provide guidelines for revising and refining criteria for existing diagnostic categories. One of Kendell's six different kinds of evidence necessary for establishing, validating, and improving clinical syndromes as diagnostic entities requires "follow-up studies establishing a distinctive course or outcome." If the criterion of increased energy can determine a BD diagnosis, it would be logical to assume youth with this symptom would experience a distinct course or outcome, compared to youth who do not have this symptom. Ideally, future studies examining the clinical validity of the increased energy criterion could group participants by those who never endorsed increased energy, compared to those who endorsed increased energy during at least one mood episode over the course of the study. Grouping participants based on whether they endorsed increased energy during their first mood episode could also contribute novel information regarding initial diagnoses and treatment course. Such studies of the increased energy criterion, and mania criteria in general, could help clarify differential diagnostic assessment, and improve the specificity of interventions for mood disorders in youth.

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4.1 Limitations

The results of this study need to be taken in the context of relevant limitations, the largest of which is the use of secondary data analyses. We were limited regarding study design and variable selection based on what was implemented in the parent COBY study. The current study aimed to explore potential clinical differences over time in participants who met DSM 5, versus DSM-IV, hypo/mania symptoms. Ideally, we would look at participants who never had increased energy, versus those who ever had increased energy, during a hypo/manic episode, but our data did not allow for such comparisons. Therefore, grouping participants into one of two energy groups had to be based on one of the three available time points that were assessed at baseline; symptom presentation at first, most recent, or most severe lifetime hypo/mania episode.. We decided to use most severe lifetime episode for multiple reasons. First, using the most severe lifetime episode increases the likelihood of detecting increased energy. Second, as the focus of the current study is on clinical outcomes observed over a 12.5 year follow-up, we indexed increased energy based on whether it was endorsed during the most severe lifetime episode (as opposed to first mood episode, or most recent mood episode), to decrease clinical variability in baseline increased energy. However, due to our decision to group participants based on most severe lifetime episode, it is possible that the participants without increased energy as part of their most severe lifetime week did have other hypo/manic episodes with increased energy. This could explain, in part, the limited between-group differences found over time.

Other study limitations based on the parent COBY study include, first, that the majority of participants were self-reported White (reflecting the race distribution for the sites participating in the study), and were recruited from clinical settings, which may limit the generalizability of the results. However, course and morbidity in non-clinically referred BD youth have been shown to be similar to those in referred populations (Lewinsohn et al., 2000). Second, despite efforts to obtain precise information, the data collected through the A-LIFE are subject to retrospective recall bias. However, the A-LIFE has been shown to have sound psychometric properties (Keller et al., 1987; Warshaw et al., 2001). Third, the primary instrument used to longitudinally track weekly mania severity, the A-LIFE PSR, does not assess elation and irritability separately. The KMRS, which we did use to specifically assess elation and irritability, was used only for the most severe week in the month prior to each follow-up (as noted above, per the parent COBY study investigators' decision), which may or may not have been during a mood episode. Fourth, the parent COBY study is naturalistic by design, in which treatment (psychosocial and psychotropic) was confounded by indication, highly variable, and interdependent with both symptomatic and psychosocial functioning outcomes. Thus, analyzing treatment in detail in the current study would be quite challenging, and likely misleading. However, we did examine inpatient hospitalization specifically, due to a prior COBY finding that greater manic symptomatology was significantly associated only with the increasing probability of inpatient hospitalization (vs other forms of treatment) (Hower et al., 2013). In the current study, we found that there were no differences between the two energy groups in inpatient utilization. Future studies specifically looking at the increased energy criterion in relation to various forms of treatment outcomes can implement study designs to reduce and adjust for the covariation of treatment with symptom severity and psychosocial functioning. This would likely result in a more

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accurate assessment of how changes in hypo/mania criteria may or may not effect treatment over the course of illness.

5. Conclusions

In summary, findings indicate clinically relevant differences on mood symptoms, family functioning, and global psychosocial functioning, between the IE+ and IE− groups at baseline. Longitudinal examination of the trajectory of the increased energy criterion over 12.5 years shows the initial distinction in energy level between groups was eliminated within five years as the level of energy in the IE+ group dropped, perhaps as part of a natural developmental process of decreasing energy levels over time. There were no significant group differences on clinical or psychosocial functioning outcomes over follow-up. Overall, the results of the current study suggest that clinically relevant differences may exist between youth who do versus do not endorse increased energy at a given time point, even though these differences do not appear to persist over time. Therefore, it would be prudent for clinicians to continue to think of endorsement of any A Criterion as important clinical information to consider when conceptualizing and monitoring mood symptoms and psychosocial functioning, with or without increased energy.

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References

Akiskal HS, Hantouche EG, Bourgeois ML, Azorin JM, Sechter D, Allilaire JF, Chatenet-Duchene L, Lancrenon S, 2001 Toward a refined phenomenology of mania: combining clinician-assessment and self-report in the French EPIMAN study. J Affect Disord 67, 89–96. [PubMed: 11869755]

Angst J, 2013 Bipolar disorders in DSM-5: strengths, problems and perspectives. Int J Bipolar Disord 1, 12. [PubMed: 25505679]

Angst J, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, Young AH, 2012 Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with DSM-IV major depressive episodes. Eur Arch Psychiatry Clin Neurosci 262, 3–11. [PubMed: 21818629]

Association AP, 2013 The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). American Psychiatric Association, Arlington, VA.

Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M, 2006 Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 63, 1139–1148. [PubMed: 17015816]

Axelson D, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, Ryan N, 2003 A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. J Child Adolesc Psychopharmacol 13, 463–470. [PubMed: 14977459]

Axelson DA, Birmaher B, Strober MA, Goldstein BI, Ha W, Gill MK, Goldstein TR, Yen S, Hower H, Hunt JI, Liao F, Iyengar S, Dickstein D, Kim E, Ryan ND, Frankel E, Keller MB, 2011 Course of

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subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. Journal of the American Academy of Child and Adolescent Psychiatry 50, 1001–1016 e1003. [PubMed: 21961775]

Bauer MS, Crits-Christoph P, Ball WA, Dewees E, McAllister T, Alahi P, Cacciola J, Whybrow PC, 1991 Independent assessment of manic and depressive symptoms by self-rating. Scale characteristics and implications for the study of mania. Arch Gen Psychiatry 48, 807–812. [PubMed: 1929771]

Benazzi F, Akiskal HS, 2003 The dual factor structure of self-rated MDQ hypomania: energized-activity versus irritable-thought racing. J Affect Disord 73, 59–64. [PubMed: 12507738]

Birmaher B, Axelson D, 2006 Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Dev Psychopathol 18, 1023–1035. [PubMed: 17064427]

Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M, 2006 Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 63, 175–183. [PubMed: 16461861]

Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M, 1999 Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. J Am Acad Child Adolesc Psychiatry 38, 1230–1236. [PubMed: 10517055]

Birmaher B, Gill MK, Axelson DA, Goldstein BI, Goldstein TR, Yu H, Liao F, Iyengar S, Diler RS, Strober M, Hower H, Yen S, Hunt J, Merranko JA, Ryan ND, Keller MB, 2014 Longitudinal trajectories and associated baseline predictors in youths with bipolar spectrum disorders. The American journal of psychiatry 171, 990–999. [PubMed: 24874203]

Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA, Davies M, 1985 The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. Arch Gen Psychiatry 42, 696–702. [PubMed: 4015311]

Cheniaux E, Filgueiras A, Silva Rde A, Silveira LA, Nunes AL, Landeira-Fernandez J, 2014 Increased energy/activity, not mood changes, is the core feature of mania. J Affect Disord 152–154, 256–261. [PubMed: 25618002]

Correll CU, Penzner JB, Frederickson AM, Richter JJ, Auther AM, Smith CW, Kane JM, Cornblatt BA, 2007 Differentiation in the preonset phases of schizophrenia and mood disorders: evidence in support of a bipolar mania prodrome. Schizophr Bull 33, 703–714. [PubMed: 17478437]

Coryell W, Turvey C, Endicott J, Leon AC, Mueller T, Solomon D, Keller M, 1998 Bipolar I affective disorder: predictors of outcome after 15 years. Journal of affective disorders 50, 109–116. [PubMed: 9858070]

Endicott J, Spitzer RL, Fleiss JL, Cohen J, 1976 The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 33, 766–771. [PubMed: 938196]

Geller B, Tillman R, Bolhofner K, Zimerman B, 2008 Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Arch Gen Psychiatry 65, 1125–1133. [PubMed: 18838629]

Goldstein BI, Birmaher B, Carlson GA, DelBello MP, Findling RL, Fristad M, Kowatch RA, Miklowitz DJ, Nery FG, Perez-Algorta G, Van Meter A, Zeni CP, Correll CU, Kim HW, Wozniak J, Chang KD, Hillegers M, Youngstrom EA, 2017 The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: Knowledge to date and directions for future research. Bipolar Disord 19, 524–543. [PubMed: 28944987]

Hedges LV, 1981 Distribution theory for Glass's estimator of effect size and related estimators. Journal of Educational Statistics 6, 107–128. .

Hower H, Case BG, Hoeppner B, Yen S, Goldstein T, Goldstein B, Birmaher B, Weinstock L, Topor D, Hunt J, Strober M, Ryan N, Axelson D, Kay Gill M, Keller MB, 2013 Use of mental health services in transition age youth with bipolar disorder. Journal of psychiatric practice 19, 464–476. [PubMed: 24241500]

Hunt J, Birmaher B, Leonard H, Strober M, Axelson D, Ryan N, Yang M, Gill M, Dyl J, Esposito-Smythers C, Swenson L, Goldstein B, Goldstein T, Stout R, Keller M, 2009 Irritability without

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elation in a large bipolar youth sample: frequency and clinical description. J Am Acad Child Adolesc Psychiatry 48, 730–739. [PubMed: 19465878]

Hunt JI, Case BG, Birmaher B, Stout RL, Dickstein DP, Yen S, Goldstein TR, Goldstein BI, Axelson DA, Hower H, Strober M, Ryan N, Swenson L, Topor DR, Gill MK, Weinstock LM, Keller MB, 2013 Irritability and elation in a large bipolar youth sample: relative symptom severity and clinical outcomes over 4 years. J Clin Psychiatry 74, e110–117. [PubMed: 23419232]

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB, 2002 The long-term natural history of the weekly symptomatic status of bipolar I disorder. Archives of general psychiatry 59, 530–537. [PubMed: 12044195]

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N, 1997 Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36, 980–988. [PubMed: 9204677]

Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC, 1987 The Longitudinal Interval Follow-up Evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 44, 540–548. [PubMed: 3579500]

Kendell R, 1989 Clinical validity. Psychological medicine 19, 45–55. [PubMed: 2657832]

Kolko DJ, Bauman BL, Bukstein OG, Brown EJ, 2007 Internalizing symptoms and affective reactivity in relation to the severity of aggression in clinically referred, behavior-disordered children. Journal of Child and Family Studies 16, 745–759.

Lewinsohn PM, Klein DN, Seeley JR, 1995 Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. Journal of the American Academy of Child and Adolescent Psychiatry 34, 454–463. [PubMed: 7751259]

Lewinsohn PM, Klein DN, Seeley JR, 2000 Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord 2, 281–293. [PubMed: 11249806]

Machado-Vieira R, Luckenbaugh DA, Ballard ED, Henter ID, Tohen M, Suppes T, Zarate CA Jr., 2017 Increased Activity or Energy as a Primary Criterion for the Diagnosis of Bipolar Mania in DSM-5: Findings From the STEP-BD Study. Am J Psychiatry 174, 70–76. [PubMed: 27523498]

Martel MM, von Eye A, Nigg J, 2012 Developmental differences in structure of attention-deficit/hyperactivity disorder (ADHD) between childhood and adulthood. Int J Behav Dev 36, 279–292. [PubMed: 25635150]

Ortiz A, Bradler K, Hintze A, 2018 Episode forecasting in bipolar disorder: Is energy better than mood? Bipolar Disord.

Scott J, Murray G, Henry C, et al., 2017 Activation in bipolar disorders: A systematic review. JAMA Psychiatry 74, 189–196. [PubMed: 28002572]

Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S, 1983 A children's global assessment scale (CGAS). Arch Gen Psychiatry 40, 1228–1231. [PubMed: 6639293]

Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA, 2016 Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania. Bipolar disorders 18, 19–32. [PubMed: 26748678]

Warshaw MG, Dyck I, Allsworth J, Stout RL, Keller MB, 2001 Maintaining reliability in a long-term psychiatric study: an ongoing inter-rater reliability monitoring program using the longitudinal interval follow-up evaluation. J Psychiatr Res 35, 297–305. [PubMed: 11591433]

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Highlights:

- Youth with vs without baseline increased energy were more likely to have bipolar I/NOS
- Youth with baseline increased energy had higher mania/depression total scores
- There was comparable frequency of increased energy between groups after 5 years
- There were no group differences on clinical/functioning outcomes over 12.5 years
- Limitations include secondary data study design; groupings based on one time point

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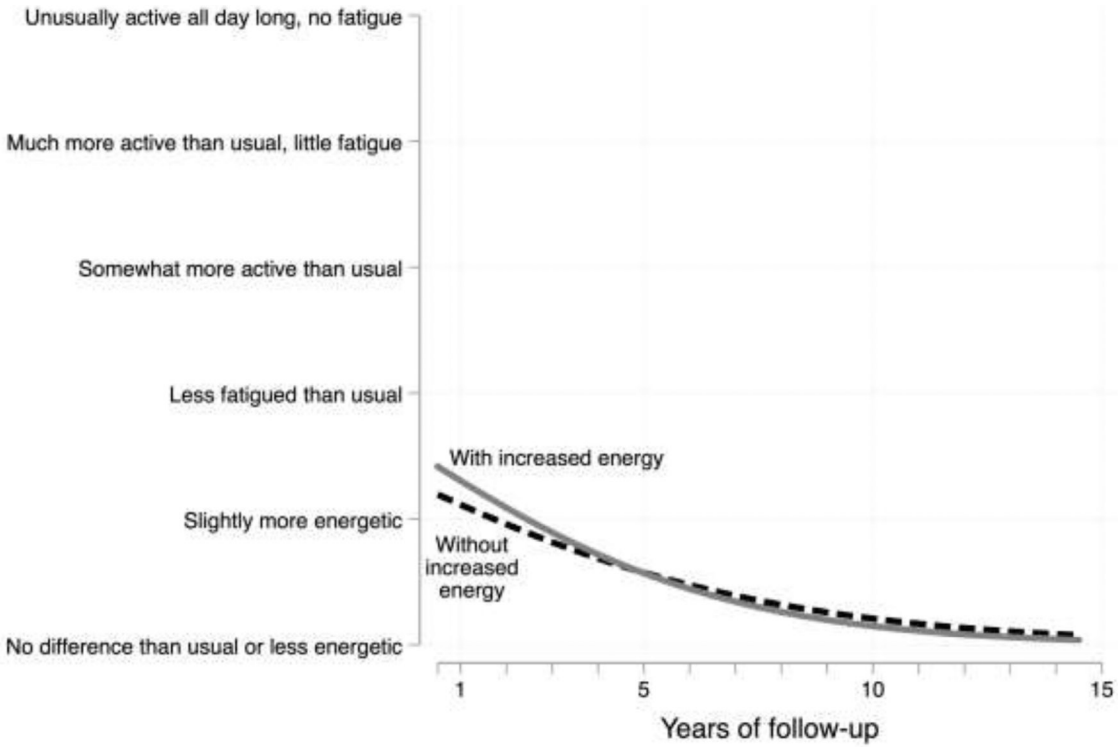

Figure 1. Generalized Linear Model (GLM) Fitted Curves for the Increased Energy and Without Increased Energy Participants Through 12.5 Years of Follow Up (N = 398).

Illustrates the model-implied mean trajectory for the unusually energetic symptom over the period of observation, from the first follow-up (six month follow-up) through the follow-up period (12.5 years), and reflects results from a mixed effect ordinal logistic regression. The outcome is an ordered categorical response variable for the six category rating on the unusually energetic symptom, which captures level of energy and fatigue, and is rated on scale from 1 (no difference than usual or less energetic) to 6 (unusually active all day long with little or no fatigue). Only the top three categories are illustrated because, on average, participants in the sample were not predicted to fall below the less fatigued than usual response category. Model-implied or expected values are plotted after accounting for effects of study site, age, and sex.

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Table 1.

Baseline Analyses of Covariance (ANCOVAs) Comparing Clinical Features of the Without Increased Energy and With Increased Energy Participants (N=430).

	IE− (N=62) *M (SD)*	IE+ (N=368) *M (SD)*	*F*	*g*
Clinical Feature				
MRS Current	16.55 (7.86)	24.17 (12.12)	22.10***	0.52
MRS Lifetime	13.77 (13.17)	30.68 (13.50)	81.99***	1.03
DRS Current	14.00 (10.53)	15.01 (10.16)	0.19	0.07
DRS Lifetime	10.31 (12.00)	20.26 (12.78)	31.00***	0.63
Age of BD Episode	9.08 (3.39)	9.23 (4.07)	0.05	0.02
Suicidal Ideation	1.29 (1.17)	1.25 (.82)	0.08	−0.01
Suicidal Acts	0.10 (.43)	0.03 (.19)	3.80	−0.01
NSSI	1.06 (1.04)	1.18 (.84)	1.42	0.02
SCARED Child	26.18 (16.26)	24.87 (18.12)	0.43	−0.06
SCARED Parent	27.38 (15.95)	24.59 (16.43)	1.50	−0.14
BCS Total	60.05 (13.30)	64.63 (14.38)	5.77*	0.27
C-GAS Current	57.66 (12.12)	53.64 (11.84)	5.60*	−0.27
C-GAS Lifetime	38.59 (10.93)	37.36 (10.19)	0.58	−0.09
Baseline Mania Symptom				
Elation	1.87 (1.47)	2.27 (1.43)	4.35*	0.05
Irritability	2.16 (1.60)	2.49 (1.53)	2.20	0.04
Grandiosity	1.42 (1.12)	1.78 (1.18)	5.80*	0.05
Decreased Sleep	1.23 (.10)	1.96 (1.60)	12.08***	0.09
Accelerated Speech	1.92 (1.43)	2.43 (1.52)	6.47*	0.06
Racing Thoughts	1.85 (1.41)	2.03 (1.40)	0.70	0.02
Flight of Ideas	1.56 (1.42)	2.19 (1.46)	10.46***	0.08
Distractibility	1.84 (1.41)	2.20 (1.38)	3.98*	0.05
Goal Activity	1.53 (1.24)	1.77 (1.26)	1.89	0.03
Hyperactivity	2.23 (1.61)	2.62 (1.61)	3.81	0.05
Poor Judgement	1.48 (1.30)	1.90 (1.41)	5.06*	0.05
Hallucinations	1.19 (1.11)	1.15 (.73)	0.13	−0.01
Delusions	0.98 (.64)	1.08 (.54)	1.63	0.01
Mood Lability	2.29 (1.57)	2.49 (1.45)	1.26	0.03
Inappropriate Laughing	1.31 (1.20)	1.74 (1.13)	9.14**	0.05
Gregariousness	1.18 (.86)	1.53 (.97)	7.28**	0.04
Increased Productivity	1.08 (1.08)	1.32 (.86)	3.40	0.03
Sharpened Creativity	0.95 (.90)	1.50 (1.03)	16.94***	0.07
Hypersexuality	1.10 (.82)	1.34 (.93)	4.09*	0.03

IE = Increased Energy; MRS = Mania Rating Scale; DRS = Depression Rating Scale; SI = Suicidal Ideation; NSSI = Non-Suicidal Self-Injurious Behaviors; C-GAS = Children's Global Assessment Scale; BD = Bipolar Disorder; SCARED = Screen for Child Anxiety Related Disorders; BCS = Behavioral Control Scale

Note:

*$p \leq .05$,

**$p \leq .01$,

$p \leq .001$; ANCOVAs include age, sex, and lifetime KSADS ADHD diagnosis as covariates; Hedges ***g is a standardized mean difference effect size statistic interpretable as a Cohen's d (0.2 small, 0.5 medium, 0.8 large).

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Table 2.

Mixed Effect Logistic Regression Analyses Outcome Profiles of the Without Increased Energy and With Increased Energy Participants Over 12.5 Years of Follow Up (N = 398).

	IE− (N=51)		IE+ (N=347)			
Outcome	**Mean**	***SD***	**Mean**	***SD***	***P***	**Effect size**
GAF	61	12	61	13	0.51	d = −0.08
Total number of hospitalizations	2.4	2.0	2.4	2.5	0.92	RR = 0.99
Percent of weeks in episode						
MDE	11	14	11	15	0.98	RR = 0.99
MAN	1.6	3.4	2.4	7.7	0.72	RR = 1.52
HYP	1.3	2.3	2.7	6.7	0.55	RR = 2.16
Any MDE, MAN, HYP	13	14	15	18	0.75	RR = 1.14
	N	**%**	**N**	**%**	***P***	**Effect size**
Suicidal ideation (ever over follow-up)	11	22%	55	16%	0.31	OR = 0.68
Suicide attempt (ever over follow-up)	1	1%	2	0.6%	0.32	OR = 0.29
NSSI (any over follow- up)	3	6%	39	11%	0.25	OR = 2.0
Any suicidal ideation, suicide attempt, or NSSI over follow-up	11	22%	71	21%	0.86	OR = 0.94

Note: OR = Odds ratio; RR = incidence rate ratio for count outcomes; NSSI = Non-Suicidal Self-Injurious Behaviors; GAF = Global Assessment of Functioning; MDE = Major Depressive Episode; MAN = Manic Episode; HYP = Hypomanic Episode