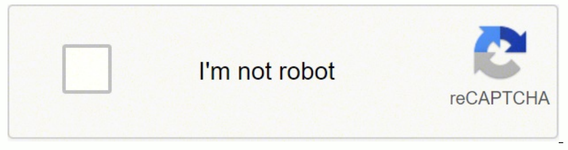

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Preliminary communication

Sensitivity and specificity of the mood disorder questionnaire and the bipolar spectrum diagnostic scale in Argentinean patients with mood disorders

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ABSTRACT

Objective: To assess the sensitivity and specificity of two self-report instruments for detection of bipolarity in a sample of Argentinean patients.
Method: Spanish versions of the MDQ and the BSDS were administered over four months at 11 sites in Argentina. Diagnoses were made using DSM-IV criteria and the MINI. The study sample consisted of patients diagnosed with Bipolar Disorder (BD) Types I, II, or NOS. BDNOS diagnoses were made using extended guidelines for bipolar spectrum symptoms. Unipolar patients were used as a control group. Of 493 patients screened, 354 completed evaluation by MDQ and MINI, and 363 by BSDS and MINI.
Results: Specificity of MDQ was 0.97 and BSDS was 0.81. MDQ sensitivity was 0.70 for bipolar type I (BD-I), 0.52 for bipolar II (BD-II) and 0.31 for bipolar not otherwise specified (BDNOS). BSDS sensitivities were 0.75, 0.70 and 0.51 respectively.
Limitations: This study was performed in specialized outpatient settings and thus its results are not necessarily representative for other clinical settings. There was not a systematic evaluation of comorbid psychiatric disease or test–retest reliability.
Conclusion: The local versions of the MDQ and the BSDS showed a sensitivity and specificity comparable to previous research. Our results indicate that in this sample, MDQ was more specific for BD and BSDS was more sensitive to detect BD-II and NOS. Since BD-I is more readily recognized than bipolar spectrum disorders, enhanced sensitivity of BSDS for soft bipolarity may be an advantage.

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Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication

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From the Intramural Research Program, Section on Developmental Genetic Epidemiology, National Institute of Mental Health (Merikangas); the International Mood Center, University of California San Diego and VA Psychiatry Service, San Diego, California (Akiskal); the Zurich University Psychiatric Hospital, Zurich (Angst); Analysis Group, Boston, Massachusetts (Greenberg); the Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston, Galveston, Texas (Hirschfeld); and the Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts (Petukhova, Kessler).

Abstract

Context—There is growing recognition that bipolar disorder (BPD) has a spectrum of expression substantially more common than the 1% BP-I prevalence traditionally found in population surveys.

Objective—To estimate the prevalence and correlates of bipolar spectrum disorder in the US population.

Design—Interviews with a nationally representative sample of English-speaking adult (ages 18+) household residents in the continental US

Participants—9,282 respondents.

Main Outcome Measures—Version 3.0 of the WHO Composite International Diagnostic Interview, a fully structured lay-administered diagnostic interview, was used to assess DSM-IV lifetime and 12 month Axis I disorders. Sub-threshold BPD was defined as recurrent hypomania without a major depressive episode or with fewer symptoms than required for threshold hypomania. Severity was assessed with the Young Mania Rating Scale for mania/hypomania and the Quick Inventory of Depressive Symptoms Self-Report for depression. Role impairment among 12-month cases was assessed with the Sheehan Disability Scales.

Results—Lifetime (and 12-month) prevalence estimates are 1.0% (0.6%) for BP-I, 1.1% (0.8%) for B P-II, and 2.4% (1.4%) for sub-threshold BPD. Comorbidity with other lifetime Axis I disorders is the norm both for threshold and sub-threshold cases. While the vast majority of people with BPD receive lifetime professional treatment for emotional problems, use of antimanic medication is much less common than use of inappropriate medications, especially in general medical settings. Clinical severity and role impairment are greater for mania than hypomania, but higher for BP-II than BP-I episodes of MDE. Although clinical severity and role impairment are greater for threshold than sub-threshold BPD, sub-threshold cases consistently have moderate-to-severe clinical severity and role impairment.

Conclusions—Inappropriate treatment of BPD is a serious problem in the U.S. population. Sub-threshold BPD is commonly occurring, clinically significant, and under-detected in treatment settings. Explicit criteria are needed to define sub-threshold BPD for future clinical and research purposes.

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brief report

Validity and reliability of the Structured Clinical Interview for Mood Spectrum - Brazilian Version (SCIMOODS-VB)

Validade e confiabilidade da versão brasileira da Entrevista Clínica Estruturada para o Espectro do Humor (SCIMOODS-VB)

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Abstract
Objective: The aim of this study was to translate the Structured Clinical Interview for Mood Spectrum into Brazilian Portuguese, measuring its reliability, validity, and defining scores for bipolar disorders. **Method:** Questionnaire was translated (into Brazilian Portuguese) and back-translated into English. Sample consisted of 47 subjects with bipolar disorder, 47 with major depressive disorder, 18 with schizophrenia and 22 controls. Inter-rater reliability was tested in 20 subjects with bipolar disorder and MDD. Internal consistency was measured using the Kuder Richardson formula. Forward stepwise discriminant analysis was performed. Scores were compared between groups; manic (M), depressive (D) and total (T) threshold scores were calculated through receiver operating characteristic (ROC) curves. **Results:** Kuder Richardson coefficients were between 0.86 and 0.94. Intraclass correlation coefficient was 0.96 (CI 95 % 0.93-0.97). Subjects with bipolar disorder had higher M and T, and similar D scores, when compared to major depressive disorder (ANOVA, $p < 0.001$). The sub-domains that best discriminated unipolar and bipolar subjects were manic energy and manic mood. M had the best area under the curve (0.909), and values of M equal to or greater than 30 yielded 91.5% sensitivity and 74.5% specificity. **Conclusion:** Structured Clinical Interview for Mood Spectrum has good reliability and validity. Cut-off of 30 best differentiates subjects with bipolar disorder vs. unipolar depression. A cutoff score of 30 or higher in the mania sub-domain is appropriate to help make a distinction between subjects with bipolar disorder and those with unipolar depression.

Descriptors: Bipolar disorder; Mood disorders; Diagnosis; Interview, psychological; Psychology, clinical

Resumo
Objetivo: *Traduzir e validar para o português a Entrevista Clínica Estruturada para Distúrbios do Humor, mensurando sua validade, confiabilidade, bem como definindo os escores para transtornos bipolares.* ***Método:*** *A entrevista foi traduzida (para o português) e novamente traduzida para o inglês. A amostra incluiu 47 indivíduos com transtornos bipolares, 47 com transtorno depressivo maior, 18 com esquizofrenia e 22 controles. A confiabilidade entre avaliadores foi testada em 20 indivíduos com transtornos bipolares e transtorno depressivo maior. A consistência interna foi mensurada por meio da fórmula de Kuder Richardson. Análise discriminante foi realizada. Escores dos diversos grupos foram comparados; limiares para mania (M), depressão (D) e valores totais foram calculados usando curvas de "receiver operating characteristic" (ROC).* ***Resultados:*** *Coeficientes de Kuder Richardson ficaram entre 0,86 e 0,94. O coeficiente de correlação intraclasse foi de 0,96 (IC 95% 0,93-0,97). Participantes com transtornos bipolares apresentaram escores M e T aumentados, e escores D semelhantes aos do grupo transtorno depressivo maior (ANOVA, p < 0,001). Os subdomínios que melhor discriminaram indivíduos com doença uni ou bipolar foram energia maníaca e humor maníaco. M apresentou a melhor área sob a curva (0,909); valores de M igual ou superiores a 30 associaram-se a sensibilidade de 91,5% e especificidade de 74,5%.* ***Conclusão:*** *Entrevista Clínica Estruturada para Distúrbios do Humor apresenta boa validade e reliabilidade. Escore de mania igual ou superior a 30 adequadamente diferencia transtornos bipolares de depressão unipolar.*

Descritores: *Transtorno bipolar; Transtornos do humor; Diagnóstico; Entrevista psicológica; Psicologia clínica*

Introduction

The Structured Clinical Interview for Mood Spectrum (SCI-MOODS) and its self-reported version (MOODS-SR) were designed to measure mood disorders as dimensional constructs.[1,2] They cover a broad range of symptoms such as the core symptoms of the DSM-IV and of ICD-10, as well as personality traits and characteristics or behaviors related to mood disorders.[3] They were developed in English and Italian simultaneously, facilitating cultural adaptation of the instrument. Furthermore, the MOODS-SR was validated in Spanish.[4] Factor analysis of the MOODS-SR helped to describe the structure of the manic

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Study (authors, year)	Study duration (weeks)	Treatment	Number of patients	Type of administration	Age of subjects (years)	Population	Outcome measures
AstraZeneca 2011[31]	8	Quetiapine 150–300 mg/day Placebo	92 100	Mono	10–17	Children and adolescents	CDRS-R, CGI-BP-S
AstraZeneca 2012[22]	8	Quetiapine 300–600 mg/day Sertraline	14 13	Combined	18–65	Adults	MADRS, CGI-BP-S, HAM-A
AstraZeneca 2012[23]	8	Quetiapine 300 mg/day Quetiapine + lithium	212 209	Mono Combined	18–65	Adults	MADRS, CGI-S, HAM-A, PSQI, Q-LES-S SF, SDS
Calabrese et al 2005[24]	8	Quetiapine 300 mg/day Quetiapine 600 mg/day Placebo	181 180 181	Mono	>18	Adults	MADRS, CGI-I, CGI-BP-S, HAM-A, PSQI, Q-LES-S SF
DelBello et al 2009[32]	8	Quetiapine 300–600 mg/day Placebo	17 15	Mono	12–18	Adolescents	CDRS-R, HAM-A, CGI-BP-S
McElroy et al 2010[25]	8	Quetiapine 300 mg/day Quetiapine 600 mg/day Paroxetine Placebo	243 244 121 124	Mono	>18	Adults	MADRS, HAM-A, CGI-BP-S, Q-LES-Q SF, SDS
Riesenberg et al 2012[26]	1	Quetiapine IR 300 mg/day Quetiapine XR 300 mg/day	69 70	Mono	18–50	Adults	Modified Bond–Lader VAS score
Suppes et al 2010[27]	8	Quetiapine 300 mg/day Placebo	133 137	Mono	18–65	Adults	MADRS, CGI-BP-S
Swartz et al 2012[28]	12	Quetiapine 50–300 mg/day Interpersonal and social Rhythm Therapy	11 14	Mono	18–65	Adults	MADRS, CGI-S
Thase et al 2006[29]	8	Quetiapine 300 mg/day Quetiapine 600 mg/day Placebo	155 151 161	Mono	18–65	Adults	MADRS, HAM-A, CGI-S, CGI-I, SDS, Q-LES-Q SF.
Young et al 2010[30]	8	Quetiapine 300 mg/day Quetiapine 600 mg/day Lithium Placebo	265 268 136 133	Mono	18–65	Adults	MADRS, HAM-A, CGI-BP-S, SDS

ating Scale	0.8
psychiatric	0.8
stionnaire (PSQ)[22]	0.9
naire (MDQ)[23]	0.7
cale (BPRS)[24]	0.6

Post hoc analysis of many psychosocial interventions for bipolar disorder suggested greater efficacy if used earlier in the illness course (104). These studies should assess the validity of the proposed predictive factors to better determine which individuals are at highest risk for conversion and therefore more likely to benefit from early interventions. Arch Gen Psychiatry 1982; 39:549–555Crossref, Medline, Google Scholar69 Tohen M, Khalsa HK, Salvatore P, et al.: Two-year outcomes in first-episode psychotic depression the McLean-Harvard First-Episode Project. Br J Psychiatry 1994; 164:831–834Crossref, Medline, Google Scholar32 Leverich GS, McElroy SL, Suppes T, et al.: Early physical and sexual abuse associated with an adverse course of bipolar illness. Other interventions, such as multifamily psychoeducational psychotherapy (110) or interpersonal and social rhythm therapy (111), have shown some preliminary but promising results in interpersonal and social rhythm therapy (111), have shown some preliminary but promising results in reducing conversion rates and symptom severity among high-risk adolescents with a positive family history of bipolar disorder. Br J Psychiatry 2013; 202:212–219Crossref, Medline, Google Scholar147 Garrido JM, Sánchez-Moreno J, Vázquez M, et al.: Evaluation of patient satisfaction in a state reference center of bipolar disorder. Similarly, in an Amish cohort of bipolar offspring (50), converters to bipolar disorder showed a higher prevalence of sensitivity, hyperalertness, anxiety, and somatic complaints during the preschool period and more mood and energy fluctuations, tearfulness, sleep disturbances, and fearfulness during school years. (145), once the most efficacious therapy is identified, further efforts should be made to ensure that at-risk populations have access to these interventions. Acta Psychiatr Scand 2014; 129:437–444Crossref, Medline, Google Scholar138 Diler RS, Goldstein TR, Hafeman D, et al.: Characteristics of depression among offspring at high and low familial risk of bipolar disorder. J Clin Psychiatry 2007; 68:789–795Crossref, Medline, Google Scholar119 Findling RL, Frazier TW, Youngstrom EA, et al.: Double-blind, placebo-controlled trial of divalproex monotherapy in the treatment of symptomatic youth at high risk for developing bipolar disorder. However, in a double-blind parallel-group placebo-controlled trial, Sharpley et al. J Psychiatr Res 2017; 85:1–14Crossref, Medline, Google Scholar100 Luo W, Phung D, Tran T, et al.: Guidelines for developing and reporting machine learning predictive models in biomedical research: a multidisciplinary view. 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By the time The American Journal of Psychiatry commemorates its 200th year of publication, we look forward to seeing that early intervention in psychiatry has been integrated in common clinical practice.References1 Mayo WJ:The aims and ideals of the American Medical Association. Arch Gen Psychiatry 2008; 65:395–407Crossref, Medline, Google Scholar95 Mesman E, Hillegers MH, Ambree O, et al.: Monocyte activation, brain-derived neurotrophic factor (BDNF), and S100B in bipolar offspring: a follow-up study from adolescence into adulthood. If replicated, in the future the risk calculator will be instrumental in the development of preventive treatments as well as for biological studies.Biological and behavioral biomarkers hold promise as objective and useful tools for identifying patients at higher risk of developing bipolar disorder (86). J Affect Disord 2017; 219:187–192Crossref, Medline, Google Scholar36 Tohen M, Greenfield SF, Weiss RD, et al.: The effect of comorbid substance use disorders on the course of bipolar disorder: a review. late in bipolar disorder. However, important potentially differentiating features such as Mitchell's bipolar signature, including features such as psychomotor-retarded melancholia and atypical depression, are not explored in many risk indices (82). Potential benefits need to be balanced against risks of preonset interventions. Staging in bipolar disorder: one step closer to precision psychiatry. Although biomarkers and staging have not yet had an impact on the official classificatory systems for mental disorders, this is a stated goal of the DSM series (87).In a sample of 98 young unaffected individuals at high familial risk of bipolar disorder and 58 healthy control subjects, the presence of maintained increased insula activation during a task involving executive and language processing could differentiate individuals at high risk of bipolar disorder who later develop depression from healthy control subjects and from those at high familial risk who did not develop a psychiatric disorder (88). Eur Neuropsychopharmacol 2016; 26:1541–1561Google Scholar130 Drago A, Serretti A, Smith R, et al.: No association between genetic markers in BDNF gene and lithium prophylaxis in a Greek sample. Furthermore, as pointed out by Lambert et al. Mayo (1861–1939) stated that "the aim of medicine is to prevent disease and prolong life; the ideal of medicine is to eliminate the need of a physician" (1). Lifestyle modifications such as smoking cessation, encouragement of physical activity, and healthy diet are indicated across the psychiatric spectrum and commonly comorbid medical disorders as well (156).Overall, this review supports the idea of the existence of an at-risk state in bipolar disorder, thereby laying the foundations for bringing early intervention to life. Data emerging from the Pittsburg Bipolar Offspring youth cohort (45) show that offspring of parents with bipolar disorder with significant symptoms of anxiety/depression, affective lability, and subsyndromal manic symptoms were at increased risk of developing bipolar spectrum disorders. JAMA Psychiatry 2017; 74:589–596Crossref, Medline, Google Scholar43 Moylan S, Gustavson K, Øverland S, et al.: The impact of maternal smoking during pregnancy on depressive and anxiety behaviors in children: the Norwegian Mother and Child Cohort Study. Bipolar Disord 2017; 19:363–374Crossref, Medline, Google Scholar31 Greenfield SF, Strakowski SM, Tohen M, et al.: Childhood abuse in first-episode psychosis. However, sensitivity and specificity limitations mean that these genetic findings are not yet robust enough to guide treatment decisions.The findings of this review support the notion of a prodromal state and a progressive course in bipolar disorder. Depressive episodes with an early onset and/or psychotic symptoms also seem to predict conversion to bipolar disorder. Potential treatments for cognitive dysfunction (cognitive enhancers) might come up in the near future and pose new ethical questions as to when and in whom to use them (129).Regarding predictors of treatment response, there are no solid results yet (130, 131), but reported results do suggest a number of regions meriting further investigation, such as the gene coding for a subunit of the ligand-gated ionotropic glutamate receptor, GluR2/GLURB (131). However, preliminary findings from the Dutch Bipolar Offspring Study indicate that the monocytes of a large proportion of bipolar patients and their offspring, particularly those who later develop a mood disorder, aberrantly express messenger RNAs of inflammatory, trafficking, survival, and mitogen-activated protein kinase pathway genes compared with healthy control subjects (94). Am J Psychiatry 2003; 160:2099–2107Link, Google Scholar41 Pasco JA, Williams LJ, Jacka FN, et al.: Tobacco smoking as a risk factor for major depressive disorder: population-based study. Since these children already present psychopathology in the form of symptoms of depression, anxiety, mood lability, or subsyndromal mania, they require existing treatments to target these symptoms—either pharmacotherapy or psychological therapies such as cognitive-behavioral therapies, family-focused therapy, self-help programs, or mental health first aid. Hence, physicians have been trying for almost a century to find early interventions that would prevent the onset of diseases, or at least change their course. J Behav Health Serv Res (Epub ahead of print, July 13, 2017) Google Scholar148 Mas S, Gasso P, Torra M, et al. Schizophr Res 2010; 120:49–53Crossref, Medline, Google Scholar142 Fernandes BS, Berk M. Expert Rev Neurother 2017; 17:277–285Crossref, Medline, Google Scholar6 Vieta E, Popovic D, Rosa AR, et al.: The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Br J Clin Psychol 2005; 44:15–27Crossref, Medline, Google Scholar76 Kwapil TR, Miller MB, Zinser MC, et al.: A longitudinal study of high scorers on the hypomanic personality scale. Including dimensional measures of mania, depression, anxiety, and mood lability; psychosocial functioning; and parental age of mood disorder, the model predicted onset of bipolar disorder with an area under the curve of 0.76. However, considering the high prevalence of mental illnesses, their significant contribution to global disease burden among young people, and their considerable impact on public health, the implementation of early interventions in psychiatry should be considered a major priority.To achieve this goal, and since early intervention focuses on known risk factors and early signs of the illness, there is a growing interest in understanding the early course of psychiatric conditions. Int J Neuropsychopharmacol 2016; 19:pyw078Crossref, Medline, Google Scholar128 Williams LJ, Pasco JA, Mohebbi M, et al.: Statin and aspirin use and the risk of mood disorders among men. Acta Psychiatr Scand 2017; 135:273–284Crossref, Medline, Google Scholar71 Verdolini N, Perugi G, Samalin L, et al.: Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features. 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Harv Rev Psychiatry 2016; 24:87–103Crossref, Medline, Google Scholar Intuitive pharmacogenetic dosing of risperidone according to CYP2D6 phenotype extrapolated from genotype in a cohort of first episode psychosis patients. Family-focused therapy, which combines psychoeducation sessions and training in communication and problem-solving skills, is the only psychological intervention tested in these populations. Moreover, greater intensity of hypomanic symptoms or earlier age at onset is associated with an increased risk of progressing to bipolar I or II disorder among children and adolescents initially meeting operationalized criteria for bipolar disorder not otherwise specified (62, 63).Some studies have focused on the predictive value of several dimensional factors and not only in categorical predictors (45, 50, 61). Hence, group psychoeducation may be particularly indicated in patients with an established diagnosis of bipolar disorder but with a limited number of recurrences (107). Bipolar Disord 2015; 17:836–848Crossref, Medline, Google Scholar57 Boschloo L, Spijker AT, Hoencamp E, et al.: Predictors of the onset of manic symptoms and a (hypo)manic episode in patients with major depressive disorder. In contrast, subthreshold (hypo)manic symptoms have emerged as a key predictor of the development of (hypo)mania in community (37, 57, 58), high-risk (59), and bipolar offspring (45, 49, 50, 60, 61) cohorts (Table 2), even after adjusting for risk factors associated with psychopathology, such as parental psychiatric morbidity (49, 58). This suggests that a single blood biomarker will likely not be useful for ascertaining diagnosis, but that a composite of several biomarkers, and probably other sources of information, will be required in order to achieve sufficient diagnostic properties for clinical utility.A newly emerging biomarker in the form of ecological momentary assessment is arising from the ability to track behavioral data through mobile devices (98, 99). Am J Psychiatry 2005; 162:1008–1010Link, Google Scholar18 Schooler N, Rabinowitz J, Davidson M, et al.: Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. This highlights the need for early interventions to prevent or at least delay the onset of the full syndromal illness during childhood, which is crucial to avoid impacts on normal developmental tasks and psychosocial or neurobiological deterioration (13) and to prevent future complications, such as the development of psychiatric comorbidities, impaired functioning, or premature death by suicide (14).Noting that The American Journal of Psychiatry is commemorating its 175th year of publication, we see early intervention in bipolar disorder as one of the cutting-edge topics in psychiatry. J Affect Disord 2005; 89:147–155Crossref, Medline, Google Scholar75 Blechert J, Meyer TD: Are measures of hypomanic personality, impulsive nonconformity and rigidity predictors of bipolar symptoms? Indeed, many of the biomarkers found in populations at risk for bipolar disorder are predictive for major psychiatric disorders in general and are common across commonly comorbid noncommunicable medical disorders, such as diabetes and cardiovascular disorders. World Psychiatry 2016; 15:186–187Crossref, Medline, Google Scholar99 W Adams Z, McClure EA, Gray KM, et al.: Mobile devices for the remote acquisition of physiological and behavioral biomarkers in psychiatric clinical research. Pharmacopsychiatry 2016; 49:229–244Crossref, Medline, Google Scholar146 Kessing LV, Hansen HV, Hvenegaard A, et al.: Treatment in a specialised out-patient mood disorder clinic v. J Clin Psychiatry 2001; 62:212–216, quiz 217Crossref, Medline, Google Scholar83 Leopold K, Ritter P, Correll CU, et al.: Risk constellations prior to the development of bipolar disorders: rationale of a new risk assessment tool. Bipolar Disord 2014; 16:505–522Crossref, Medline, Google Scholar85 Hafeman DM, Merranko J, Goldstein TR, et al.: Assessment of a person-level risk calculator to predict new-onset bipolar spectrum disorder in youth at familial risk. PLoS One 2014; 9:e106871Crossref, Medline, Google Scholar58 Papachristou E, Oldehinkel AJ, Ormel J, et al.: The predictive value of childhood subthreshold manic symptoms for adolescent and adult psychiatric outcomes. Furthermore, in an independent prospective study of 73 patients treated with lithium monotherapy for a period of up to 2 years, carrying the response-associated alleles was associated with a significantly lower rate of relapse (132). When focusing only on patients diagnosed with psychotic depression, it has been found that conversion to bipolar disorder is mainly related to early age at onset (67, 68), functional impairment (67), mixed features (69, 71), and previous hypomanic symptoms (72).FIGURE 1. Bipolar Disord 2010; 12:494–503Crossref, Medline, Google Scholar111 Goldstein TR, Fersch-Podrat R, Axelson DA, et al.: Early intervention for adolescents at high risk for the development of bipolar disorder: pilot study of Interpersonal and Social Rhythm Therapy (IPSRT). Can Fam Physician 1974; 20:65–68Medline, Google Scholar4 Berk M, Berk L, Dodd S, et al.: Stage managing bipolar disorder. Neurotox Res 2011; 19:279–285Crossref, Medline, Google Scholar137 Grande I, Magalhães PV, Chendo I, et al.: Staging bipolar disorder: clinical, biochemical, and functional correlates. J Psychiatr Res 2016; 72:22–29Crossref, Medline, Google Scholar48 MacCabe JH, Lambe MP, Cnattingius S, et al.: Excellent school performance at age 16 and risk of adult bipolar disorder: national cohort study. Acta Psychiatr Scand 2014; 129:275–285Crossref, Medline, Google Scholar45 Hafeman DM, Merranko J, Axelson D, et al.: Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. Biological risk factors include family history of bipolar disorder or neurodevelopmental factors such as child developmental delay. Am J Psychiatry 2016; 173:695–704Link, Google Scholar46 Preisig M, Strippoli MF, Castelao E, et al.: The specificity of the familial aggregation of early-onset bipolar disorder: A controlled 10-year follow-up study of offspring of parents with mood disorders. Key considerations include the individual's knowledge, autonomy, and right to choose, ideally in an environment of stigma-free treatment (103).Effective psychotherapeutic interventions, usually better received by patients and with a more favorable benefit–risk profile, can be an attractive first step in early intervention, although their effectiveness at these early stages needs to be determined (83). Consequently, this translates into a need for screening for attenuated mania-like symptoms when assessing young patients seeking help for mood lability, anxiety, depression, or behavioral disorders, especially among bipolar offspring (138). Psychotherapies are not free of side effects (112); at early stages, when the diagnosis is not established, emphasis on diagnoses should be avoided, and it is more useful to target identified symptoms and helpful strategies (113). In a sample of help-seeking youths, individuals meeting the bipolar at-risk criteria transitioned significantly more to first-episode (hypo)mania than the group screening negative for the criteria (81). Am J Psychiatry 1967; 123:1058–1068Link, Google Scholar16 Eaton WW, Badawi M, Melton B: Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. Recent public outrage at institutional childhood sexual abuse and campaigns to address this in many countries are an exemplar of a policy approach that may have an impact on a critical risk (33). Eur Neuropsychopharmacol 2017; 27:647–656Google Scholar149 Solé B, Vieta E, Martinez-Aran A. J Affect Disord 2012; 136:1000–1010Crossref, Medline, Google Scholar84 Correll CU, Olvet DM, Auther AM, et al.: The Bipolar Prodrome Symptom Interview and Scale-Prospective (BPSS-P): description and validation in a psychiatric sample and healthy controls. BMC Med 2017; 15:80Crossref, Medline, Google Scholar87 Vieta E: DSM-5.1. Acta Psychiatr Scand 2016; 134:187–188Crossref, Medline, Google Scholar88 Whalley HC, Sussmann JE, Romaniuk L, et al.: Prediction of depression in individuals at high familial risk of mood disorders using functional magnetic resonance imaging. Arch Pediatr Adolesc Med 2004; 158:773–780Crossref, Medline, Google Scholar35 Barbuti M, Pacchiarotti I, Vieta E, et al.: Antidepressant-induced hypomania/mania in patients with major depression: evidence from the BRIDGE-II-MIX study. Brain Behav Immun 2016; 58:11–17Crossref, Medline, Google Scholar97 Hayes JF, Khandaker GM, Anderson J, et al.: Childhood interleukin-6, C-reactive protein and atopic disorders as risk factors for hypomanic symptoms in young adulthood: a longitudinal birth cohort study. Consequently, psychiatry has focused more on tertiary prevention, that is, in the use of therapies aiming to minimize the consequences of clinically established disease rather than to prevent its occurrence (3). In fact, more than 20 years ago, The American Journal of Psychiatry published one of the first articles discussing the role of prodromes and precursors in major depression (16); 10 years later the journal published the first paper proposing early intervention to prevent substance abuse in first-episode bipolar disorder (17) and a landmark trial indicating that first-episode psychosis could be treated with lower dosages of antipsychotics than are used in multiple-episode psychoses (18). Moreover, preliminary findings indicate that bipolar offspring with an aberrant inflammatory state or changes in the volume or activity of the amygdala may be more vulnerable to developing a mood disorder, suggesting a potential role for these alterations as putative biomarkers for disease prediction in individuals at genetic risk (121, 139).However, even if there is a promising emerging set of putative prodromal symptoms, biomarkers, and environmental risk factors, the possible additive or synergistic associations between all these factors remains a mystery (121). Novel bioinformatic techniques, such as machine learning approaches, present a valuable ally in the field of early intervention to overcome such limitations (142, 143).Early intervention is an ideal breeding ground for new randomized clinical trials looking for the most efficacious treatment strategy for early stages. Am J Psychiatry 2013; 170:542–549Link, Google Scholar53 Akiskal HS, Downs J, Jordan P, et al.: Affective disorders in referred children and younger siblings of manic-depressives: mode of onset and prospective course. Some pilot studies have assessed the protective properties of valproate sodium and quetiapine against the onset of mania, with mixed results (117–119). J Affect Disord 2017; 207:95–101Crossref, Medline, Google Scholar80 Youngstrom EA, Freeman AJ, Jenkins MM: The assessment of children and adolescents with bipolar disorder. Am J Psychiatry 2001; 158:1265–1270Link, Google Scholar67 Østergaard SD, Straszek S, Petrides G, et al.: Risk factors for conversion from unipolar psychotic depression to bipolar disorder. Moreover, the assessment of subsyndromal manic symptoms requires trained professionals, as subsyndromal symptoms are difficult to ascertain when assessing children or if comorbid disorders are present. In a prospective general-population U.K. birth cohort childhood study, higher levels of the systemic inflammatory marker IL-6 in childhood were associated with hypomanic symptoms in young adulthood, even after adjusting for sociodemographic variables, past psychological and behavioral problems, body mass index, and maternal postnatal depression (97).Nevertheless, most of the identified alterations in peripheral blood in ultra-high-risk populations are shared between different psychiatric disorders, potentially predicting the onset of bipolar disorder, depression, or schizophrenia, but alone they are not able to reliably predict occurrence of bipolar disorder over another disorder. Higher scores on the depression scale of the General Behavior Inventory (74), higher scores on the Hypomanic Personality Scale (75, 76), and positive subthreshold hypomanic symptoms identified by the Hypomania Checklist–32 (77) were related to an increased risk of future mood disorder among bipolar offspring. Life events have been proposed as triggers of future bipolar disorder (25), but results are controversial. (125) did not find any impact of folic acid supplementation on the incidence of mood disorder in a youth sample at increased familial risk of mood disorder. Br J Psychiatry 2008; 193:322–326Crossref, Medline, Google Scholar42 Quinn PD, Rickert ME, Weibull CE, et al.: Association between maternal smoking during pregnancy and severe mental illness in offspring. Acta Psychiatr Scand 2017; 136:362–372Crossref, Medline, Google Scholar72 Salvatore P, Baldessarini RJ, Khalsa HM, et al.: Predicting diagnostic change among patients diagnosed with first-episode DSM-IV-TR major depressive disorder with psychotic features. Bipolar Disord 2015; 17:39–49Crossref, Medline, Google Scholar96 Snijders G, Schiweck C, Mesman E, et al.: A dynamic course of T cell defects in individuals at risk for mood disorders. The interaction between risk factors and prodromal symptoms may lead to bipolar disorder, but the exact mechanisms remain unknown.The above predictors are based on studies that focus on groups as a whole, but they do not inform about the individual risk of developing bipolar disorder. However, we cannot deny that further efforts are required to advance on the difficult road of primary prevention. For very early stages, promoting and enhancing cognitive reserve may be one way to go (151–154).Early intervention strategies in bipolar disorder face the lack of specificity of prodromal symptoms, as evidence emerging from studies performed in populations at ultra-high risk for psychosis indicate that there might be a common risk syndrome for diverse major psychiatric illnesses prior to the development of full symptoms more characteristic of any particular disease (141). Arch Gen Psychiatry 2003; 60:497–502Crossref, Medline, Google Scholar23 Bortolato B, Köhler CA, Evangelou E, et al.: Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. Early Interv Psychiatry 2016; 10:381–389Crossref, Medline, Google Scholar27 Kemner SM, Mesman E, Nolen WA, et al.: The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study. This dynamic course fits in the model of clinical staging proposed by several authors (14, 134–137), which assumes that illnesses progress from an at-risk stage to a late and resistant stage.A positive family history of bipolar disorder, particularly if the parents have early-onset bipolar disorder, is the most significant risk factor for developing a bipolar spectrum disorder. Thinking ahead: executive dysfunction in bipolar disorder. For instance, valproate sodium has been associated with reproductive–endocrine abnormalities and should be used with caution in women of childbearing age (122, 123). However, reliable clinical scales to assess prodromal symptoms are still lacking. Am J Psychiatry 2000; 157:220–228Link, Google Scholar14 Duffy A, Alda M, Hajek T, et al.: Early stages in the development of bipolar disorder. J Affect Disord 2015; 183:45–48Crossref, Medline, Google Scholar38 Duffy A, Horrocks J, Doucette S, et al.: The developmental trajectory of bipolar disorder. Considering the impact of life events in illness trajectory, lifetime sexual abuse seems to be related to a worse course of bipolar disorder (29–32). In turn, the Child Behavior Checklist–Bipolar seems useful for predicting comorbid and impairing psychopathology rather than any one specific DSM-IV diagnosis (73, 78). Very gradual dosage escalation and cautious use of pharmacotherapy, potentially augmented by pharmacogenetics if positive data emerge, may help treatment choice when pharmacological treatment becomes necessary. Rev Bras Psiquiatr 2017; 39:88–89Google Scholar143 Salvador R, Radua J, Canales-Rodríguez EJ, et al.: Evaluation of machine learning algorithms and structural features for optimal MRI-based diagnostic prediction in psychosis. Acta Psychiatr Scand 2014; 129:323–327Crossref, Medline, Google Scholar102 Rosa AR, Magalhães PV, Czepielewski L, et al.: Clinical staging in bipolar disorder: focus on cognition and functioning. Eur Psychiatry 2013; 28:21–29Google Scholar7 Baldessarini RJ, Bolzani L, Cruz N, et al.: Onset-age of bipolar disorders at six international sites. Psychol Med 2017; 47:23–33Crossref, Medline, Google Scholar98 Hidalgo-Mazzei D, Murru A, Reinares M, et al.: Big Data in mental health: a challenging fragmented future. J Affect Disord 2013; 150:363–369Crossref, Medline, Google Scholar55 Lewinsohn PM, Klein DN, Seeley JR: Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. Int J Psychiatry Clin Pract 2010; 14:154–157Crossref, Medline, Google Scholar131 Perlis RH, Smoller JW, Ferreira MA, et al.: A genomewide association study of response to lithium for prevention of recurrence in bipolar disorder. Hum Psychopharmacol 2011; 26:451–459Crossref, Medline, Google Scholar121 McNamara RK, Nandagopal JJ, Strakowski SM, et al.: Preventative strategies for early-onset bipolar disorder: towards a clinical staging model. Bipolar Disord 2009; 11:391–400Crossref, Medline, Google Scholar10 Bellivier F, Golmard JL, Rietschel M, et al.: Age at onset in bipolar I affective disorder: further evidence for three subgroups. Moreover, treatment with mood stabilizers or antipsychotics has known short- and long-term adverse effects (120), so their use as first-line treatment in at-risk youths might not be recommendable (121). J Affect Disord 2014; 167:306–311Crossref, Medline, Google Scholar126 McGorry PD, Nelson B, Markulev C, et al.: Effect of ω-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO Randomized Clinical Trial. Am J Psychiatry 2017; 174:417–418Link, Google Scholar134 Berk M, Conus P, Lucas N, et al.: Setting the stage: from prodrome to treatment resistance in bipolar disorder. The pharmacogenetics of pharmacodynamic pathways, such as P450 enzymes and blood-brain barrier polymorphisms, is being explored as a predictor of antidepressant response (133), although not yet for mood stabilizers. Thus, the efficacy of omega-3 fatty acids in high-risk populations needs further investigation (127). Main Risk Factors of Conversion From Major Depressive Disorder to Bipolar DisorderIn summary, parental bipolar disorder, especially early-onset (e.g.,

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