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Research report

Validation of the "rule of three", the "red sign" and temperament as behavioral markers of bipolar spectrum disorders in a large sample

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ABSTRACT

Background: Akiskal proposed the "rule of three" for behavioral indicators with high specificity for bipolarity in patients with major depression episodes. We evaluated these distinctive behaviors in controls and subjects with major depression or bipolar disorder.
Methods: data was collected in the BRAINSTEP project with questions on general behaviors, style and talents. Univariate analysis was first conducted in 36,742 subjects and confirmatory multivariate analysis in further 34,505 subjects (22% with a mood disorder). Odds ratios were calculated adjusting for age.
Results: Univariate analysis showed that 29 behavioral markers differentiated bipolar subjects from those with unipolar depression. The most robust differences in those with bipolarity (ORs >4) were ≥ 3 religion changes, ≥ 3 marriages, cheating the partner regularly, having ≥ 60 lifetime sexual partners, pathological love, heavy cursing, speaking ≥ 3 foreign languages, having ≥ 2 apparent tattoos, circadian dysregulation and high debts. Most behaviors were expressed in a minority of patients (usually around 5–30%) and usually the "rule of three" was the best numerical marker to distinguish those with bipolarity. However, multivariate analysis confirmed 11 of these markers for differentiating bipolar disorder from unipolar depression (reversed circadian rhythm and high debts for both genders, ≥ 3 provoked car accidents and talent for poetry in men, and frequent book reading, ≥ 3 religion changes, ≥ 60 sexual partners, pathological love ≥ 2 times, heavy cursing and extravagant dressing style in women).
Limitations: Self-report data collection only.
Conclusions: These behavioral markers should alert the clinician to perform a thorough investigation of bipolarity in patients presenting with a depressive episode.

1. Introduction

The differential diagnosis between major depression and bipolar disorders currently relies exclusively on the presence of mania for bipolar type I and hypomania for bipolar type II. This imposes a major problem since hypomania is often unrecognized by the patient, undetected by the clinician, may not reach the four-day cut-off criteria defined in DSM-V, or has not yet emerged in the course of the mood disorder. Thus, these guidelines suggest that patients who present with a depressive episode should always be treated for unipolar major depression unless a spontaneous (*i.e.* not induced by antidepressants, stimulants or drugs of abuse) (hypo)manic episode has developed. However, there is substantial evidence that around half of the patients with a depressive episode belongs to the bipolar spectrum or meet bipolarity specifiers (Akiskal and Benazzi, 2005; Angst et al., 2010, 2011).

In clinical practice, information on course (*e.g.* age at onset, number of episodes, mood fluctuations), family history, temperament, comorbidities (*e.g.* bulimia), intrusive hypomanic symptoms within the depressive episode (*i.e.* mixed features) and response to medication are useful for identifying bipolar spectrum disorders (Akiskal et al., 1977; Akiskal et al., 1995; McElroy et al., 2005; Benazzi, 2006; Angst et al., 2011), with or without documented (hypo)mania. These features transcend official diagnoses but enable the clinician to provide adequate treatment to these

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patients. Unfortunately, even the currently available diagnosis of cyclothymia has been understudied and subdiagnosed, and when detected in patients with an episode of major depression, should direct treatment towards mood stabilization besides targeting the acute episode.

Akiskal (2005) advanced the field of differential diagnosis of mood disorders by focusing on behavioral markers distinctively associated with bipolarity. Based on extensive clinical observations and case records, he listed several behaviors that putatively have low sensitivity but high specificity for the diagnosis of bipolarity, *i.e.* they are relatively rare, but when present, strongly indicate a bipolar disorder. These biographic signs and behaviors followed the pattern named as "rule of three" given their repeated and cyclic nature (*e.g.* three or more weddings, religions, foreign languages…). Another facet of the "rule of three" is the presence of a triad of specific characteristics, such "mood lability", "energy activity" and "daydreaming" (Akiskal et al., 1995). Also, the "red sign" denoted a tendency of individuals with bipolarity for ornamentation and flamboyance, as in preference for items with vibrant colors (Akiskal, 2005). To understand the rationale for this kind of approach, it is important to consider that different aspects of the mind, such as mood, personality, cognition and behavior tend to operate in concert and share neurobiological substrates (Lara and Akiskal, 2006; Anderson, 2010), meaning that certain predispositions to particular states (*e.g.* hypomania), may also be manifest at the trait behavioral level. Also, temperament and personality of those with bipolar disorders differ from healthy controls and those with major depression, typically showing more cyclothymic and novelty-seeking traits (Nowakowska et al., 2005). Thus, given the externalized and unstable nature of bipolar disorders and their underlying temperaments, it is reasonable to conceive that their biography and behaviors would show distinctive patterns and features.

We have developed a web-based system to anonymously evaluate the general population in Brazil, aiming to have a large sample with a thorough assessment of behavioral, psychological and psychiatric measures. In this enterprise, called the Brazilian Internet Study on Temperament and Psychopathology (BRAINSTEP), we included questions about the behavioral markers suggestive of bipolarity proposed by Akiskal (2005) and other features observed in our clinical practice. The current study sought to investigate behavioral markers and temperament variables distinctively associated with bipolar individuals in comparison to controls and individuals with major depression.

Given that Akiskal's (2005) approach for using behavioral indicators of bipolarity has received insufficient attention in the literature (Fulford 2008; Manning, 2010; Culpepper 2010; Strakowski et al. 2011), in the present research we seek to test his views on a large sample of subjects in a different culture. As his proposal includes many behavioral markers, we first analyzed each marker separately using an univariate model, which would better represent a clinical perspective. Next, in an independent sample, we performed a multivariate model to find out the core behavioral markers. We considered that abehavioral marker to be validated when significantly more expressed in a bipolar disorder group compared to controls and unipolar major depression in the multivariate analysis.

2. Methods

2.1. Ethics

The Ethics Committee of Hospital São Lucas (PUCRS) approved the protocol of this study. All participants gave their electronic informed consent before entering the system. This form was created to fulfill the requirements of the National Health Council of Brazil (Resolution 196/1996) and the Code of Ethics of the World Medical Association (Declaration of Helsinki). Probands could cancel their voluntary and anonymous participation at any moment without justification. Personal information was sent via a secure and encrypted connection and was stored behind a firewall. Our system guaranteed anonymity by coding the e-mail addresses when data was stored, so that no one (even research staff) could have access to the e-mails of specific participants.

2.2. Sampling and procedures

The data presented are part of the BRAINSTEP web-based survey (Lara et al., 2012a): a noncommercial, advertisement-free website in Brazilian Portuguese (www.temperamento.com.br), which was broadcast on national TV news programs in Brazil and in major city newspapers. Volunteers reported demographic variables, which psychiatric diagnoses they had received from mental health professionals, and answered several self-report instruments, including the Affective and Emotional Composite Temperament Scale (AFECTS, Lara et al., 2012b), the Adult Self-Report Inventory (ASRI; Gadow et al., 2004), the Hypomania/Mania Symptom Checklist (HCL-32; Angst et al., 2005), and the questions on behavior and style described here.

To ensure data validity and to promote participation and adherence, participants were promptly informed about the scientific purposes of the study, that participation was anonymous, free of charge, and that they would receive a 6–7 page report on their temperament profile and the probability of having a positive screening for 19 psychiatric disorders currently and in the past. They were also informed that the whole system could take 2–3 h to complete; however, they could interrupt the process and come back to where they had stopped for a period of one week after they had started. After accepting participation, a password to log in was sent to their email address with a copy of instructions.

To ensure reliability of the data, questions checking for attention were inserted within the instruments. Also, at the end of the system there were two specific questions on the degree of attention, sincerity and seriousness of the volunteer while responding to the instruments. Only those who stated being attentive, sincere and serious throughout the study and had correct answers in the attention validity items were included. Finally, to evaluate the validity status of the diagnosis of bipolarity received by the mental health professional, the mean scores of the HCL-32 and the past manic symptoms from the ASRI were used.

All subjects that completed the instruments used in this study with age ranging from 18 to 65 were included, resulting in a total of 86,135 volunteers (26.9% males). After the exclusion of those who failed in the validity checks, the final sample was composed of 71,247 subjects, with 19,412 males (27.3%, 31.9 ± 10.6 years old) and 51,835 females (77.7%, 31.6 ± 10.4 years old). This sample was further divided into two independent sets: the first set, with 36,742 participants, was used to explore and identify individual behavioral markers associated with bipolarity via univariate statistics. The second set, composed of 34,505 participants, was used to confirm and test the pertinence of selected behavioral markers for bipolarity via multivariate statistics. Fig. 1 depicts the methodological approach regarding the sample.

The prevalence of mood disorders and mean age for each diagnostic group are shown in Table 1. Diagnostic groups were defined according to diagnoses ever received by participants from mental health professionals. Therefore, there were those with major depression diagnosis only, bipolar disorder diagnosis only or both diagnoses. Those with major depression only were further divided according to their affective temperament (internalized/stable or externalized/unstable – see below). Individuals without