

Universidade Católica de Pelotas

AUGUSTO DUARTE FARIA

ALTERAÇÕES DO RITMO BIOLÓGICO NO TRANSTORNO DE HUMOR BIPOLAR

Pelotas

2013

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Tese apresentada ao Programa de Pós-Graduação em Saúde e Comportamento da Universidade Católica de Pelotas, como requisito parcial para obtenção do grau de Doutor em Saúde e Comportamento.

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Pelotas

2013

ALTERAÇÕES DO RITMO BIOLÓGICO NO TRANSTORNO DE HUMOR BIPOLAR

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INTRODUÇÃO GERAL

Apesar dos avanços no tratamento do transtorno bipolar, uma proporção significativa de pacientes experienciam sintomas incapacitantes entre os episódios e as taxas de recaída são elevadas. Estas circunstâncias sugerem que existe uma necessidade crítica para se alcançar a compreensão dos gatilhos de recaída e trata-los com intervenções específicas, validadas empiricamente. Os distúrbios no Ritmo Biológico estão entre os correlatos mais importantes de episódios de humor e de uma recuperação inadequada, mas, infelizmente, ainda pouco se sabe sobre sua importância para o surgimento e manutenção da doença.

Este trabalho foi elaborado como requisito para obtenção do grau de doutor em Saúde e Comportamento pela Universidade Católica de Pelotas (UCPel) e é dividido em três partes, sendo a primeira o projeto do estudo, a segunda os artigos elaborados durante o curso de doutorado, e a terceira compreende as considerações finais.

A respeito dos artigos elaborados, incluídos na Parte II desse volume, o primeiro artigo tratou especificamente sobre alterações do Ritmo Biológico, em um estudo de caso-controle derivado de amostra populacional, através de uma escala clínica objetiva, a *Biological Rhythm Interview Assessment in Neuropsychiatry* (BRIAN). O segundo trabalho teve como objetivo avaliar a influência de um modelo de Psicoeducação na regulação do Ritmo Biológico em uma amostra de jovens adultos, dentro da mesma amostra populacional.

A terceira parte desse volume traz as considerações finais, a fim de retomar as hipóteses do projeto e dos referidos artigos, sumarizando os principais achados do trabalho como um todo.

O volume foi organizado dessa maneira a fim de apresentar os dados encontrados em resposta às questões de pesquisa, com uma mensuração quantitativa de alterações do Ritmo Biológico no transtorno bipolar em comparação com controles saudáveis e a avaliação da capacidade que uma intervenção manualizada em regular esse ritmo em tratamento combinado e tratamento medicamentoso padrão para o transtorno.

PARTE I – Projeto

1 IDENTIFICAÇÃO

1.1. Título

Alterações do ritmo biológico no transtorno de humor bipolar

1.2. Doutorando

Augusto Duarte Faria

1.3. Orientador

Prof. Dra. Karen Jansen

1.4. Programa de Pós-Graduação

Saúde e Comportamento (PPGSC) – Doutorado

1.5. Instituição

Universidade Católica de Pelotas (UCPel)

1.6. Linha de Pesquisa

Psicologia e Saúde

1.7. Data

Setembro de 2013

2 DELIMITAÇÃO DO PROBLEMA

2.1. Introdução/Justificativa

Alterações no ritmo biológico estão entre as características etiológicas sugeridas para o Transtorno Bipolar e estão associados ao comprometimento funcional da doença,¹ com danos que podem persistir mesmo durante a remissão, sintomas subsindrômicos, episódios de humor e aumentam o risco de recaída.^{2,3} As mudanças podem ocorrer, principalmente, devido aos distúrbios do sono,⁴ alterações de rotina, ausência de indicadores externos de tempo externo ("zeitgebers")⁵ e eventos de vida estressantes.⁶ Estas interrupções dos ritmos biológicos são, provavelmente, um dos correlatos mais proeminentes do início de episódios maníacos agudos.^{7,8} A instabilidade circadiana configura, por conseguinte, a vulnerabilidade central da doença bipolar.⁹

Estudos sugerem que uma desregulação no ritmo biológico pode estar relacionada ao desenvolvimento, progressão, recaída, bem como o agravamento do resultado a longo prazo no transtorno bipolar e também em outros transtornos do humor, como o Transtorno Depressivo Maior e Transtorno Afetivo Sazonal.^{10,11,12} O Ritmo Biológico é um conceito que avalia, ao mesmo tempo, variações cíclicas de funções fisiológicas e comportamentais.¹³ Uma disfunção no Ritmo pode levar a uma perda de ordenação do tempo interno e alterações neurobiológicas, alterando os padrões de produção e secreção de serotonina, noradrenalina, dopamina, cortisol e melatonina, o que pode agravar estados de humor.^{10,14}

Observações clínicas da influência do prejuízo no ritmo podem ser vistas em mudanças no humor ao longo do dia e as alterações do ciclo sono-vigília, que podem levar a problemas de funcionamento e da qualidade de vida.¹⁵ Apesar dos avanços na pesquisa do Transtorno Bipolar, uma parcela significativa de indivíduos ainda sofre de sintomas incapacitantes entre os episódios e as taxas de recaída são elevadas,¹⁶ o que faz com que a compreensão do porquê isso acontece um tema de alta prioridade. É plausível acreditar que uma perturbação do ritmo atue como gatilho para uma recaída.^{1,17} No entanto, a avaliação do construto do Ritmo Biológico é possibilidade recente e precisa de mais investigações.

2.2. Objetivos e hipóteses

1º ARTIGO

Biological rhythm disruption in Bipolar Disorder: a case-control study in a population-based sample of young adults

Objetivo: Avaliar a regulação do Ritmo Biológico em indivíduos com transtorno bipolar de uma amostra de base populacional de jovens adultos, em comparação com dois grupos- controle: no primeiro, sujeitos sem histórico prévio de transtornos do humor; no segundo, indivíduos diagnosticados com depressão unipolar.

Hipótese: Os indivíduos com Transtorno Bipolar terão maior alteração no ritmo biológico do que aqueles com depressão e controle “saudáveis”.

2º ARTIGO

The influence of Psychoeducation on regulating biological rhythm in a sample of patients with bipolar disorder: a randomized clinical trial

Objetivo: Comparar dois modelos de intervenção para pacientes bipolares: uma intervenção padrão, medicamentosa, e uma intervenção combinada, de medicação e um modelo breve e manualizado de Psicoeducação.

Hipótese: Os sujeitos atendidos pelo modelo combinado terão maior regulação do Ritmo Biológico do que aqueles submetidos ao tratamento padrão.

3 MÉTODO

3.1. Delineamento

Ensaio clínico randomizado aninhado a um estudo transversal com três grupos pareados, tendo como população alvo jovens de 18 a 24 anos selecionados por conglomerados em um estudo de base populacional na cidade de Pelotas/RS.

3.2. Amostra: tamanho e seleção

O tamanho amostral foi estimado para o estudo transversal de base populacional através do programa Epi-Info 6.04d,¹⁸ com nível de confiança de 95%, hipótese de prevalência de 8% para episódio maníaco ou hipomaníaco¹⁹ e maior prevalência esperada de 10%. No intuito de minimizar o efeito que a seleção amostral por conglomerado pode ter sobre a prevalência do desfecho, o tamanho amostral foi multiplicado por dois. Sendo assim, chegamos a um N amostral mínimo de 1388 jovens.

Para o estudo transversal a seleção amostral foi realizada por conglomerados, no período de agosto de 2007 a dezembro de 2008, considerando a população de 39.667 jovens na idade alvo e a divisão censitária atual de 448 setores na cidade de Pelotas de acordo com o Instituto Brasileiro de Geografia e Estatística.²⁰ A fim de garantir a inclusão da amostra necessária, 89 setores censitários foram sorteados sistematicamente. A seleção dos domicílios nos setores sorteados foi realizada segundo uma amostragem sistemática, sendo o primeiro domicílio a residência da esquina pré-estabelecida pelo IBGE como início do setor, o intervalo de seleção foi determinado por um pulo de dois domicílios entre os sorteados.

Ao finalizar o estudo transversal foram identificados 1762 jovens de 18 a 24 anos entre os 89 setores censitários incluídos, porém 202 (11,5%) jovens se recusaram a participar do estudo ou não foram localizados após a identificação. Sendo assim, a amostra constituiu-se de 1560 jovens, destes 117 (7,5%) apresentaram episódio de mania atual ou passada.²¹ Entretanto, foi possível parear por sexo, idade e classificação socioeconômica, 93 jovens com episódio maníaco, 93 com episódio depressivo e 93 controles populacionais (correspondentes ao restante dos jovens avaliados, independente da presença ou ausência de outros transtornos que não os transtornos de humor).

Após a confirmação diagnóstica, os jovens com transtorno bipolar serão

convidados a participar de um ensaio clínico randomizado para dois modelos de intervenção: psicoeducação + medicação (intervenção combinada) e intervenção padrão.

3.3. Instrumentos e variáveis

3.3.1 Características da amostra

Para o estudo de base foi construído um questionário com as seguintes variáveis: idade, sexo, estado civil, escolaridade, trabalho, auto-relato quanto à cor da pele ou etnia, história de transtorno psiquiátrico familiar, utilização de medicação e história de internação. A avaliação econômica dos participantes foi realizada de duas maneiras: através da renda familiar declarada pelos entrevistados e da aplicação de uma escala de avaliação socioeconômica. O Índice socioeconômico será avaliado através do Índice Nacional de Economia,²² com base no total de bens materiais e de escolaridade do chefe da família, entre outros itens. As classes socioeconômicas são divididas em três níveis (alto, médio e baixo) para a população brasileira de acordo com o Censo Demográfico de 2000.

3.3.2 Mini Internacional Neuropsychiatric Interview 5.0 (MINI)

Na visita domiciliar, foi realizada uma entrevista diagnóstica padronizada breve - *Mini Internacional Neuropsychiatric Interview* (MINI).²³ Esta entrevista de curta duração – 15 a 30 minutos – é destinada a utilização na prática clínica e de pesquisa, e visa classificar os entrevistados de forma compatível com os critérios do DSM-IV e CID-10. Através dela foi possível averiguar a presença de episódio depressivo e maníaco/hipomaníaco.

3.3.3 Structured Clinical Interview DSM-IV (SCID)

É uma entrevista diagnóstica semi-estruturada criada a partir do DSM-IV, será utilizada para o diagnóstico de transtorno bipolar e depressão. A tradução e a adaptação desta entrevista clínica para o idioma português, apresentam em geral, boa confiabilidade, com coeficiente de Kappa excelente (0,87) para os transtornos de humor.²⁴

Como esforço para refinar e validar os instrumentos de campo, para que sejam o

mais próximo possível do padrão de diagnóstico, a SCID será utilizado em uma sub-amostra de calibração do estudo, assim como tem sido realizado em grandes estudos populacionais.^{25, 26}

3.3.4 *Hamilton Depression Rating Scale (HDRS)*

A gravidade dos sintomas depressivos foi medida pela Escala de Avaliação de Depressão de Hamilton (HDRS), um instrumento de 17 itens que permite a criação de uma variável discreta, na qual os pontos mais elevados correspondem a uma maior gravidade dos sintomas. A consistência interna varia 0,83-0,94. A confiabilidade da escala entre avaliadores tem sido consistente em vários estudos.²⁷

3.3.5 *Young Mania Rating Scale (YMRS)*

Para avaliar a intensidade dos sintomas maníacos utilizou-se a Escala Young para Avaliação de Mania (YMRS), uma escala de 11 itens, escolhida por sua alta confiabilidade na medição de níveis de gravidade da mania e coeficiente de validade. A versão validada para o Brasil, que tem um nível de confiança ainda melhor do que o original, teve sua consistência interna avaliada pelo α de Crombach, calculada pela análise de variância aplicada aos onze itens da escala.²⁸ A partir da matriz de co-variância, resultante, um $\alpha = 0,67$ foi obtido para a escala como um todo e uma $\alpha = 0,72$ para cada item normalizada ($P < 0,001$).

3.3.6 *Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN)*

A avaliação do ritmo biológico foi feito usando a *Biological Rhythm Interview of Assessment in Neuropsychiatry* (BRIAN). Esta escala foi projetado para oferecer uma medida confiável, validada e padronizada do Ritmo Biológico, com escores clinicamente compreensíveis para os investigadores. Os 18 itens são divididos em três áreas específicas (sono/ritmo social, atividade, padrão alimentar), que são classificadas segundo uma escala de 4 pontos: 1 (sem dificuldade) e 4 (muito difícil). A validade e a confiabilidade da versão em Português da BRIAN incluem informações sobre a sua análise fatorial e como as áreas foram selecionadas.²⁹

3.4. Seleção e treinamento de pessoal

O treinamento do estudo consistiu na apresentação da equipe e explicação dos

aspectos metodológicos e logísticos do estudo, assim como da leitura e discussão do questionário, manual do entrevistador e da entrevista diagnóstica padronizada breve. A equipe responsável pela identificação dos domicílios foi orientada sobre a forma de proceder na chegada às residências, a importância de identificar-se, como solicitar permissão para a realização da entrevista, o local da casa adequado para a mesma, modo de abordagem no domicílio, bem como sobre os procedimentos éticos da investigação.

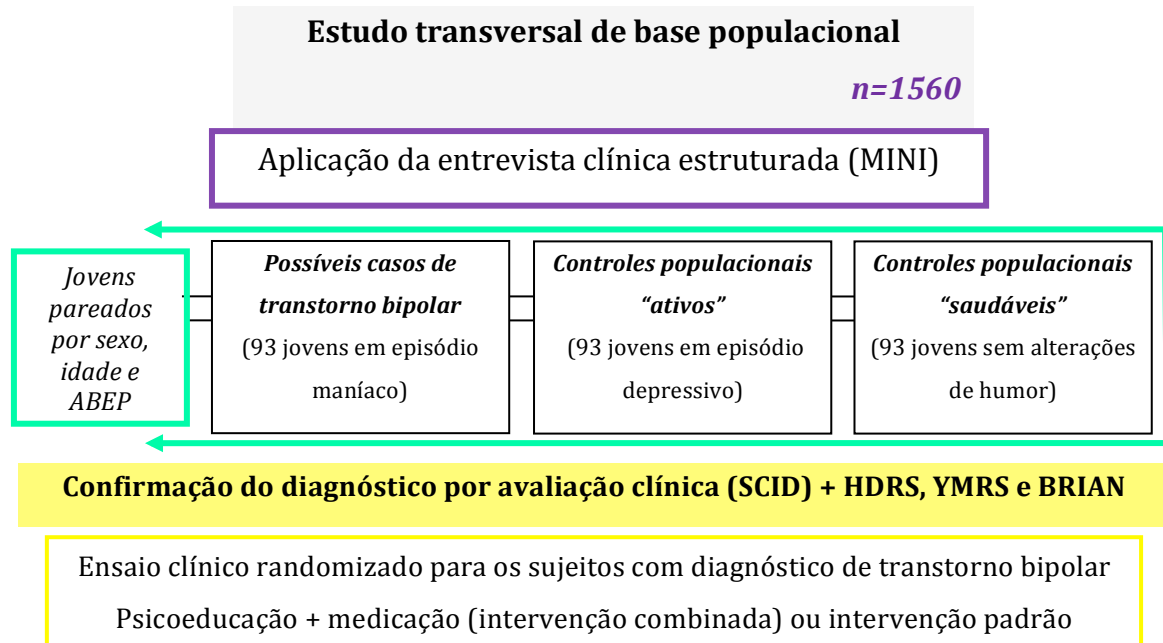
Os entrevistadores do estudo transversal de base populacional foram acadêmicos do Centro de Ciência da Vida e da Saúde da Universidade Católica de Pelotas. A seleção dos entrevistadores ocorreu de acordo com a prática na realização do treinamento, histórico acadêmico e a disponibilidade de tempo para execução das entrevistas. Os mesmos passaram por um treinamento que teve por objetivo a familiarização com o questionário e as fases de aplicação.

No estudo de caso-controle, o treinamento para a realização das entrevistas clínicas foi ministrado em conjunto pela equipe da instituição principal (UCPel) e do Laboratório de Psiquiatria Molecular da Universidade Federal do Rio Grande do Sul (UFRGS). As avaliadoras foram três psicólogas treinadas para realizar a entrevista de acordo com os critérios do DSM-IV apresentados na SCID-CV.

Para o ensaio clínico randomizado serão selecionados acadêmicos do último ano do curso de psicologia da UCPel. O treinamento ocorrerá durante o período de um mês, no qual serão apresentados os objetivos da psicoeducação, a forma de aplicação e os objetivos de cada sessão do modelo de intervenção.

3.5. Logística da coleta de dados

Figura 1: Delineamento e avaliações a serem realizadas.



3.6. Aspectos éticos

O estudo transversal e o caso-controle, vinculados ao projeto de doutorado, foram aprovados pelo Comitê de Ética em Pesquisa (CEP) da UCPel de acordo com o protocolo 2006/96. O ensaio clínico para o transtorno bipolar foi aprovado pelo mesmo CEP sob o protocolo de número 2009/24.

Este projeto garante respeitar a todos os princípios éticos estabelecidos pelo Conselho Nacional de Saúde na Resolução Nº 196 de 10 de Outubro de 1996. Os jovens receberão informações sobre os objetivos da pesquisa e assinarão um “Consentimento livre e esclarecido”. Será assegurado o direito à confidencialidade dos dados e o cuidado na utilização das informações nos trabalhos escritos, de modo que os participantes não possam ser identificados.

3.7. Processamento e análise dos dados

Após a codificação dos instrumentos, será realizada dupla entrada dos dados no programa Epi-Info 6.04d. Para que possa ser realizada uma checagem automática dos dados no momento da digitação será utilizado o comando *check*, além disso, será testada no mesmo software a consistência da digitação comparando as duas entradas de dados.

Para análise dos dados serão utilizados os programas SPSS 13.0 e STATA 9.

3.8. Orçamento

Na tabela 2, pode-se observar o custo do estudo, porém cabe ressaltar que este conta com o apoio financeiro do CNPQ.

Tabela 1: Despesas de custeio para os projetos de pesquisa em questão.

Despesas de Custeio	Quantidade	Valor Individual	Valor Total (R\$)
<i>Transversal de base populacional</i>			
Material de Consumo			
Vale transporte para as entrevistas	3524	1,85 ^a	6.519,40
Cópias dos questionários	1560	0,75	1.170,00
Serviços de terceiros			
Captação da amostra (setores)	89	20,00	1.780,00
Entrevista de avaliação domiciliar	1560	8,00	12.480,00
Sub-total (R\$) →			21.949,40
<i>Caso-controle</i>			
Material de Consumo			
Vale transporte para as avaliações	460	2,00 ^b	920,00
Cópias dos instrumentos de avaliação	230	1,30	299,00
Serviços de terceiros			
Avaliação clínica	230	50,00	11.500,00
Sub-total (R\$) →			12.719,00
Total (R\$) →			34.668,40

^a Valor do vale transporte em 2008.

^b Valor do vale transporte em 2009.

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PARTE II – Artigos

1º ARTIGO – BIOLOGICAL RHYTHM DISRUPTION IN BIPOLAR DISORDER: A CASE-CONTROL STUDY IN A POPULATION-BASED SAMPLE OF YOUNG ADULTS

Biological rhythm disruption in Bipolar Disorder

ABSTRACT

Objectives: The aim of this report is to evaluate biological rhythm disruption in a case-control study nested in a population-based cross-section of people aged 18 to 24 years old. *Methods:* Caseness was confirmed with the Structured Clinical Interview for DSM-IV (SCID). The *Biological Rhythm Interview Assessment in Neuropsychiatry* (BRIAN) was used to measure biological rhythm. The severity of depressive symptoms was measured with the *Hamilton Depression Rating Scale* (HDRS), and to assess the intensity of manic symptoms we utilized the *Young Mania Rating Scale* (YMRS). The Linear Regression was elaborated to account for potential confounders. *Results:* The sample consisted of 231 subjects. Of these, 94 were control subjects, 82 had major depression and 55 had bipolar disorder (33 type I and 22 type II). Irregular biological rhythm was associated with a diagnosis of bipolar disorder (40.40 ± 9.78 ; $p < 0.001$) and major depression (36.39 ± 9.22 ; $p > 0.001$) when compared with healthy controls (27.67 ± 6.88). Furthermore, the severity of depression symptoms was highly correlated with the total BRIAN scores ($r = 0.592$; $p > 0.001$). *Discussion:* This population-based study further reinforces the notion that bipolar disorder and major depression are associated with impairment in biological rhythm.

Keywords: Bipolar disorder; Biological Rhythm; Depression; Epidemiology.

INTRODUCTION

Biological Rhythm disruptions are among the characteristics suggested for Bipolar Disorder (BD) etiology and are associated with functional impairment of the disease,¹ with damages that can persist even during remission, such as subsyndromal symptoms, mood episodes and risk of relapse.^{2, 3} The changes may occur mainly due to sleep disturbances,⁴ routine alterations,¹ absence of external time indicators (“zeitgebers”)⁵ and stressful life events.⁶ These biological rhythm disruptions are, probably, one of the most prominent correlates of onset of acute manic episodes.^{7, 8} The circadian instability configures, therefore, the core vulnerability of bipolar disorder.⁹ Besides BD, previous studies suggest that a dysregulation in biological rhythm may also be linked to the development, progression, relapse as well as worsening of long-term outcome of other mood disorders, such as Major Depressive Disorder and Seasonal Affective Disorder.^{10,11,12} Biological rhythm is an all-embracing concept and evaluates, at the same time, cyclical variations of physiological and behavioral functions.¹³ Rhythm disfunction lead to a loss of internal time ordering internal and neurobiological alterations that can exacerbate mood states by changing patterns of serotonin, norepinephrine, dopamine, cortisol and melatonin secretion.^{10,14} Clinical observations of the rhythm impairment influence can be seen in mood swings throughout the day and sleep-wake cycle changes, what leads to poor functioning and quality of life.¹⁵

Despite the progress in BD research, a significant portion of subjects still suffers from disabling symptoms between episodes and the relapse rates are high,¹⁶ what makes the understanding of what makes this happen a high priority topic. It is plausible to believe that a rhythm disruption acts as a relapse trigger.^{1,17} However, the construct evaluation is only a new possibility and needs further investigations.

The objective of this study was to evaluate the biological rhythm regulation in subjects with bipolar disorder of a population-based sample of young adults compared with two control groups: in the first one, subjects without previous history of mood disorders, and in the second, individuals diagnosed with unipolar depression. Our hypothesis, according with the scientific literature in the field, is that bipolar subjects group will present greater biological rhythm disturbance than the depression and control groups.

METHODS

This is a case-control study nested in a population-based cross-section of people aged 18 to 24. Full details on the larger study have been published elsewhere.¹⁸ Briefly, the sample consisted of 1560 participants from 18 to 24 year old living in urban Pelotas, southern Brazil. Sample selection was performed by clusters, in the period of August'07 to December'08, considering a population of 39,667 people in the targeted age range in the current census of 448 sectors.¹⁹ In order to ensure the necessary sample inclusion, 89 census-based sectors were systematically drawn. After the subjects were identified, study subjects signed the informed consent and answered to a questionnaire to collect socio-demographic data, drug misuse, as well as a structured diagnostic interview. The project was approved by the Ethic Committee on Research of Catholic University of Pelotas (UCPel).

As an initial psychopathology screen, the whole population underwent the Mini-International Neuropsychiatric Interview.²⁰ For the purposes of the current study, we attempted to recruit every person with a past or current history of a manic or hypomanic episode – the target sample – from the population-based study. Additionally, two groups of control subjects were recruited: in the first one, people without any history of affective disorder were randomly selected and matched for sex, age and socioeconomic situation – i.e., a healthy control sample. Importantly, we did not exclude people on account of any other mental disorders. The second control group, was formed with those with a current depression but no past history of (hypo)mania. This was, thus, an active control group. Of these, we were able to obtain data of 231 subjects (83% of the originally intended sample).

In order to improve diagnosis reliability, we further used the Structured Clinical Interview for DSM-IV (SCID). This interview model is based *on the* Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision (DSM-IV-TR), with a translation and adaptation to Portuguese that presents, in general, good reliability, with excellent Kappa coefficient (0.87) for mood disorders.²¹ The interviews were conducted by two Ph.D students, who underwent intensive training under supervision of a senior researcher. Some subjects were reclassified after this interview, which was used as the group-defining criterion for the study.

The evaluation of the biological rhythm was made using the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN). This scale was designed to offer a

reliable, validated e standardized measure of biological rhythm, with scores clinically understandable for researchers. The 18 items are divided in three specific areas (activity, sleep/social rhythm and eating pattern) that are rated using a 4-point scale: 1 (no difficulty) and 4 (very difficult). It has excellent reliability, both in terms of internal consistency ($\alpha = 0.93$) and test-retest ($ICC = 0.98$). Total BRIAN scores were highly correlated with the global Pittsburgh Sleep Quality Index (PSQI) score ($\rho=0.77$; $p<0.001$). The validity and reliability of the Portuguese BRIAN version are described by Giglio et al,²² including information about its factor analysis and how the areas were selected.

The severity of depressive symptoms was measured with the Hamilton Depression Rating Scale (HDRS), a 17-item scale that enables the creation of a discrete variable, in which the higher scores correspond to a higher severity of the symptoms. The internal consistency ranges from 0.83 to 0.94. The scale reliability between raters has been consistent in several studies.²³ To assess the intensity of manic symptoms we utilized the *Young Mania Rating Scale* (YMRS), a 11-item scale chosen for its high reliability in measuring severity levels of mania and validity coefficient. The Brazilian validated version,²⁴ which has an even better reliability level than the original, had its internal consistency assessed by Crombach's α , calculated using analysis of variance applied to the eleven items of the scale. From the resulting co-variance matrix, an $\alpha = 0.67$ was obtained for the scale as a whole and an $\alpha = 0.72$ for each standardized item ($P<0.001$). Information on drug misuse was obtained with the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), validated to Portuguese.²⁵

Descriptive analyses are presented in percentage, means and standard deviation, or median and interquartile range. Demographic and clinical characteristics were analyzed using chi-square, ANOVA and Kruskal-Wallis test as indicated in the tables. BRIAN scores presented a normal distribution and were tested by parametric test ANOVA with Bonferroni for multiple comparisons between the participants with mood disorders according to the presence of current symptoms. Additionally, the correlation between depressive symptoms and biological rhythm was measured by simple linear regression.

RESULTS

The total sample of the case-control study consisted of 231 subjects, where 55 had bipolar disorder (33 type I and 22 type II), 82 had major depression and 94 were control subjects, all comparable regarding age and education years, with female sex been underrepresented in the control group. The demographic and clinical data regarding the groups are presented in Table 1.

The different BRIAN scores in the participants with mood disorders was observed according to the presence of current symptoms ($F=25.9$; $p<0.001$). The Bonferroni test for multiple comparisons demonstrated that BRIAN scores were increased in bipolar disorder subjects with current symptoms when compared to controls ($p<0.001$) and subjects with remitted major depression ($p=0.001$) (Table 2). Moreover, we found increased BRIAN scores in major depression subjects with current symptoms ($p<0.001$) and remitted bipolar subjects ($p=0.010$) when compared to healthy controls. (Figure 1). Depressive symptoms showed a positive correlation with biological rhythm alteration in subjects with major depression ($r=0.396$; $B=0.460$; $p<0.001$ in Figure 2A) and bipolar disorder ($r=0.480$; $B=0.539$; $p<0.001$ in Figure 2B).

DISCUSSION

The evidence found in this research indicate an association between biological rhythms disturbances and mood disorders, according with the study hypothesis. In this sample, Bipolar disorder-subjects experience greater biological rhythm disruption when compared to controls and remitted depression-subjects. These findings are consistent with previous investigations what suggests that biological rhythm dysregulation may plays a core role in the pathophysiology of bipolar illness.^{26,27,28} The most affected BRIAN domains were sleep and social rhythm, ie, subjects not only had sleep-wake disruption, but also loss in personal activities. This, according to the Social Zeitgeber Theory,²⁹ can ignite a series of biological abnormalities, making them more likely to relapse.

Moreover, we also found that current symptoms depression-subjects presented greater rhythm impairment than controls. This association was demonstrated in previous works,^{26, 30} but remain unclear if rhythm disturbances lead to depressive symptoms or they are consequences of the mood symptoms.

As previously mentioned, scientific knowledge about the harmful aspects of biological rhythm dysregulation asserts that individuals vulnerable to mood disorders

find it difficult to adapt to changes in circadian rhythms,^{13, 31} at the same time that mood disorders may have their etiology associated with circadian rhythm disorders (such as phase advances, sleep disorders and *zeitgebers*).^{6,11,32} Thus, a vicious cycle is created and the mood dysregulation affects, for example, the quality, quantity and stability of sleep by modifying the circuit of dopamine and serotonin, hence affecting mood,³³ which, linked to an increase of the allostatic load³⁴ may lead to an illness worsening.

The stability of the relationship between exogenous and endogenous factors is essential to a normal mood state. The desynchronization of biological rhythms with the external world can result in mood swings and contribute to a chronobiological susceptibility to mood episodes.³⁵ Thus, efforts to stabilize the biological rhythm must be part of therapeutical approaches for mood disorders,¹³ highlighting early identification of disruptions as part of the treatment.

Here we must emphasize the positive aspects of the study, such as the use of an objective instrument of clinical utilization and the population-based sample (without previous treatment), which allows generalization of the data and replicability to new investigations. The biological rhythm structure assessed by BRIAN scale is consistent with the current body of theory regarding sleep and rhythm disturbances in bipolar disorder.²² Since biological rhythm is a broad concept, the scale allows to present changes in different dimensions of the construct. As a limitation of this investigation we must point out one aspect, that BRIAN relies on the subjects self-report, which lacks reliability.

To date, etiological determinants of the mood spectrum disorders remain poorly understood. The growing numbers of reports that have investigated the relationship between these disorders and circadian genes, chronotypes and circadian physiological processes strongly suggest that chronobiology can help clarify the underlying mechanism of mood disorders. Thus, it is pertinent that biological rhythm should be targeted for new interventions, since rhythm dysfunction proved to be a predictor of impairment and relapses for subjects with mood disorders and the majority of subsyndromal symptoms (such as fatigue and sleep) can start a vicious cycle that feeds back rhythm disruptions. Our results also suggest that these investigations must include evaluations of stability-based biological rhythm interventions, focusing on psychoeducation and regular routines, reported to be effective in preventing relapses and improving functioning in BD.^{36,37}

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Table 1

Sample characteristics described by groups.

Characteristic	Healthy control sample	Major depression	Bipolar disorder	<i>p</i> -value
N	94	82	55	
Age*	22.4 ±2.7	21.8 ±2.0	21.8 ±2.2	0.108
Female sex**	57.4%	76.8%	74.5%	0.012
Years of education*	9.7 ±3.1	8.9 ±2.8	8.8 ±3.6	0.173
Current medication				
Mood stabilizers**	0	2.4%	3.6%	0.215
Antipsychotics**	0	0	3.6%	0.040
Antidepressants**	1.1%	2.4%	5.5%	0.265
Benzodiazepines**	1.1%	1.2%	3.6%	0.462
Any **	2.1%	12.2%	16.4%	0.002
Lifetime tobacco misuse**	24.5%	37.8%	45.5%	0.023
Lifetime alcohol misuse**	26.6%	37.8%	38.2%	0.198
Lifetime illicit substance misuse**	9.6%	23.2%	16.4%	0.049
Current State**				<0.001
Euthymia	100%	23.2%	20%	
Depressive episode	0	76.8%	60%	
Mania/mixed episode	0	0	20%	
HDRS score***	0 (0 – 1)	13 (7 – 19)	15 (10 – 21)	<0.001
YMRS score***	0 (0 – 0)	0 (0 – 0)	0 (0 – 8)	<0.001

HDRS: Hamilton Depression Rating Scale. YMRS: Young Mania Rating Scale.

* Percentile, Chi-square test.

** Mean and standard deviation, One-way ANOVA test.

*** Median and interquartile range, Kruskal–Wallis test.

Table 2

Biological Rhythm Interview Assessment in Neuropsychiatry (BRIAN) for controls, major depression and bipolar groups.

Biological rhythm	Controls n=94 (A)	Major depression n=82 (B)	Bipolar disorder N=55 (C)	ANOVA		Post-hoc (Bonferroni)
				F	p	
Sleep/social*	14.1 (4.2)	19.0 (5.1)	21.3 (5.6)	41.09	<0.001	A ≠ B, C / B ≠ C
Activity*	6.4 (1.9)	8.1 (2.7)	9.0 (3.0)	21.72	<0.001	A ≠ B, C
Eating pattern*	7.1 (2.7)	9.4 (3.2)	10.0 (3.0)	20.41	<0.001	A ≠ B, C
Total*	27.7 (6.9)	36.5 (8.9)	40.4 (9.8)	45.83	<0.001	A ≠ B, C / B ≠ C

Percentile, Chi-square test.

Figure 1

Biological Rhythm Interview Assessment in Neuropsychiatry (BRIAN) scores in the participants with mood disorders according to the presence of current symptoms.

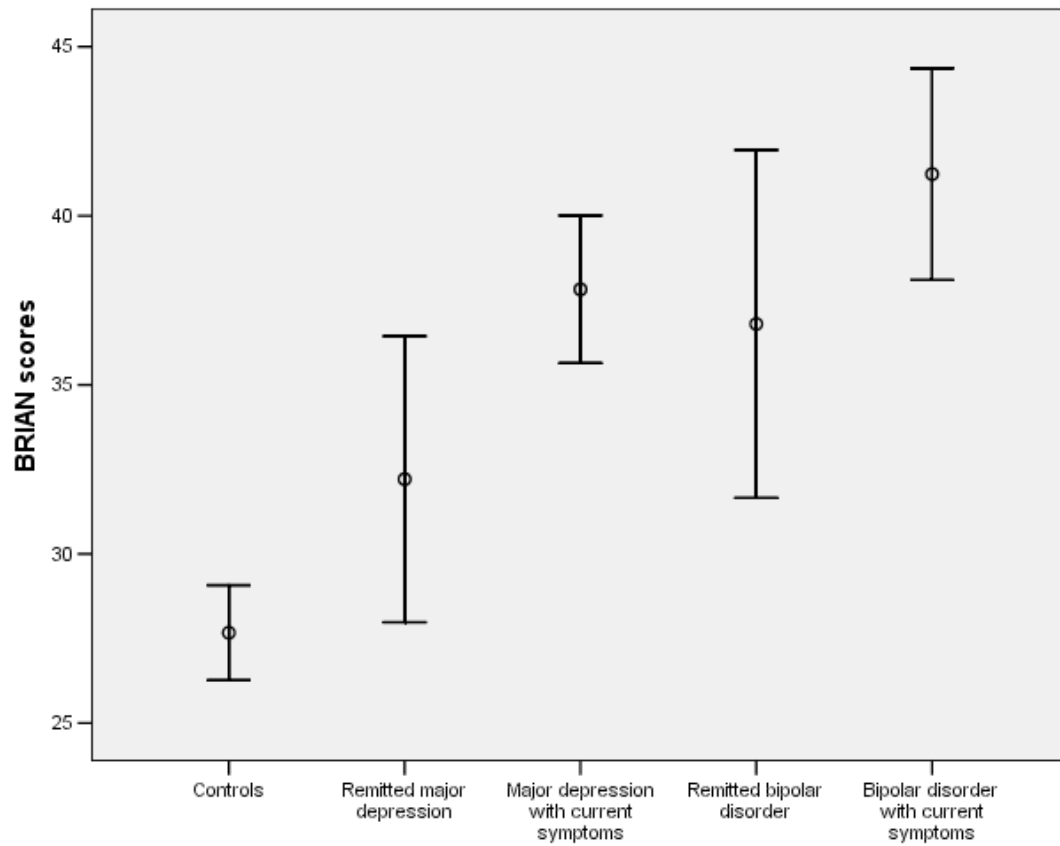
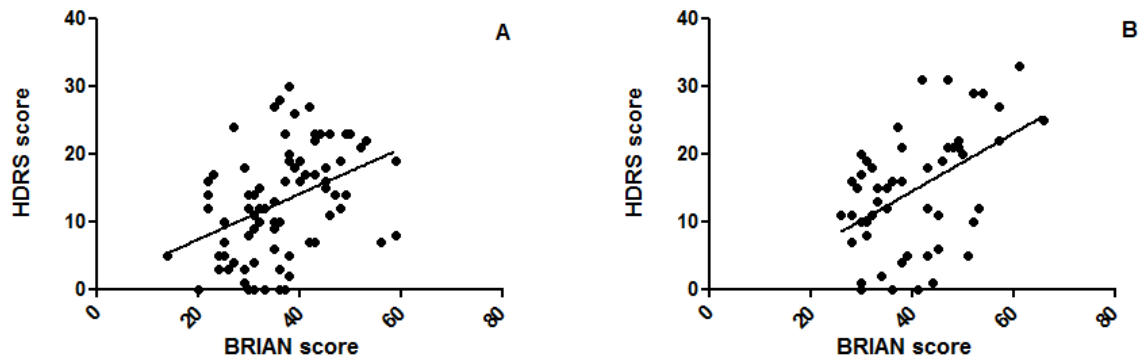


Figure 2 - Correlation between depressive symptoms and biological rhythm (A = Subjects with major depression and B = Subjects with bipolar disorder).



2º ARTIGO – THE INFLUENCE OF PSYCHOEDUCATION ON REGULATING BIOLOGICAL RHYTHM IN A SAMPLE OF PATIENTS WITH BIPOLAR DISORDER: A RANDOMIZED CLINICAL TRIAL

Psychoeducation and biological rhythm in bipolar patients

ABSTRACT

Introduction: Changes in biological rhythm are among the various characteristics of bipolar disorder and have long been associated with the functional impairment of the disease. There are only a few viable options of psychosocial interventions that deal with this specific topic and one of them is Psychoeducation, a model that, although it has been used by practitioners for some time, only recent studies have showed its efficacy in clinical practice. Aim: To assess if patients undergoing psychosocial intervention in addition to a pharmacological treatment could have a better regulation of their biological rhythm than those who were only using medication. Method: This study is a randomized clinical trial that compares a standard medication intervention to an intervention combined with drugs and psychoeducation. The evaluation of the biological rhythm was made using the Biological Rhythm Interview of Assessment in Neuropsychiatry, a 18-item scale divided in four areas (sleep, activity, social rhythm and eating pattern). The combined intervention consisted in medication and a short-term psychoeducation model summarized in a protocol of six individual sessions of one hour each. Results: The sample consisted of 61 patients, but during the study, there were 14 losses to follow-up. Therefore, the final sample consisted of 45 individuals (26 for standard intervention and 19 for combined). The results founded showed that, in this sample and time period evaluated, the combined treatment of medication and psychoeducation had no statistically significant impact on the regulation of biological rhythm, when compared to a standard pharmacological treatment. Conclusion: Although the changes in biological rhythm were not statistically significant during the time period evaluated in this study, it is noteworthy that the trajectory of the score shows a tendency of improvement, what may indicates a contribution even though it may take longer than expected.

Keywords: Psychoeducation; Biological Rhythm; Bipolar Disorder.

INTRODUCTION

Changes in biological rhythm are among the various characteristics of bipolar disorder (BD) and *have* long been associated with the functional impairment of the disease,¹ with damages that may persist even during remission, such as subsyndromic symptoms and risk of relapse.² These changes occur mainly due to sleep disturbances³ (that can be related to allelic mutations on clock genes⁴), changes in routine¹ and stressful life events.⁵ It has also been suggested that bipolar subjects secrete abnormal levels of melatonin and are hypersensitive to light changing their sleep pattern.⁶ Disruptions in the biological rhythm of subjects with bipolar disorder can trigger acute episodes of mood with, for example, clear links between sleep disturbances and mania.⁷ A poor repertoire of coping skills to face social rhythm disruptions may compromise the *maintenance of a euthymic state* of the subjects, resulting in a looping of failed attempts of regulation.

Although pharmacotherapy is an indispensable primary option for the treatment of BD, it is interesting to offer viable options of psychosocial interventions in order to improve pharmacological treatment adherence, coping skills and increasing the patient's quality of life.⁸ These interventions are increasingly recognized as an essential component in the treatment of BD.^{9,10} Successful psychosocial interventions for unipolar depression such as Adjunctive Family Therapy,^{11,12} Cognitive Behavioral Therapy¹³ and Interpersonal and Social Rhythm Therapy¹⁴ were adapted for bipolar disorder and evaluated by trials, being associated with greater symptoms stabilization and change of habits. However, not all are equally effective and long-term effects are not convincing.

Among all psychosocial interventions, Psychoeducation (PE), has been one of the most used and is recommended by several guidelines^{15,16} as a first choice for BD due to its appeal to a wider population, because of its straightforward and cost-effective profile. PE is recommended for pharmacological adherence enhancement, knowledge and awareness of the disease.¹⁷ It is particularly helpful for subjects to learn how to detect prodromal signs of the disease and, consequently, to prevent relapses.^{18, 19} Although PE is an intervention model that has been used by practitioners for some time, only recently studies with reliable methodology showing its efficacy in clinical practice were published.²⁰⁻²³ A recent systematic review by Batista²⁴ identified a total of 13 randomized clinical trials evaluating PE in bipolar disorder. Briefly, these studies evaluated PE in different samples (BD-only subject, relatives/caregivers or both) in both

group and individually. The number of sessions ranged from 5 to 21 meetings and the follow-ups were from 6 months to 5 years. The results of the review indicates that PE is an intervention particularly effective to decrease the relapse rate (both manic and depressive) and to improve overall social functioning. However, as pointed by the authors, the mechanism of action of PE remains unknown. Their primary hypothesis says that teaching lifestyle regularity is the main aspect and may play a role in the relapses prevention due to early detection of prodromal symptoms.

Bipolar disorder is a neuroprogressive disease, longitudinally associated with increased severity and an accelerated disability. One of the concepts that attempt to explain why bipolar disorder worsens over time is Allostatic Load (AL). Briefly, AL discusses the cumulative effects of an overload of the adaptative systems due to the typical chronic overactivity of the disease.²⁵ The AL increases progressively as stressors and mood episodes occur over time and is connected to the cognitive impairment of BD that includes attention, executive function and verbal memory.²⁶

Since the first mood episodes are happening sooner (with an age-of-onset of 23 years) and severe symptoms are unfolding earlier is there a possible higher severity of bipolar disorder in younger generations,²⁷ which raises the question whether a psychosocial intervention applied in a younger sample with less years of disease, fewer mood episodes and, therefore, less cognitive impairment can have a different impact on regulating their biological rhythm. For this purpose, we carried out a study with young adults, ages between 18 and 29 years, diagnosed with BD, where we compared a standard intervention (pharmacological with mood stabilizers) and a combined intervention of drugs and a short-term psychoeducation model.²⁸ Although studies that showed the effectiveness of psychoeducation for the treatment of BD^{18, 29} had a similar design (randomized clinical trial), the sampling and the intervention design were significantly different. We do not know of any study that has evaluated a short-term individual psychoeducational intervention for bipolar subjects in a sample formed exclusively of young adults with no previous treatment.

AIM

The aim of this study was to assess if subjects undergoing psychosocial intervention in addition to a pharmacological treatment could have a better regulation of their biological rhythm than those who were only using medication.

METHOD

Design and Setting

This study is a randomized clinical trial that evaluated the influence of psychoeducation on regulating the biological rhythm of individuals with Bipolar II Disorder by comparing a standard medication intervention to an intervention combined with drugs and psychoeducation. The project was approved by the Ethic Committee on Research of Catholic University of Pelotas (UCPel), according to protocol No. 2009/24, and all participants signed the informed consent.

In order to assure the necessary sample size to estimate the effectiveness of the interventions, the trial was advertised in public health care units, psychosocial care centers, outpatient clinics and hospitals of the city. The subjects recruited in these places were selected as follows.

Those who agreed to participate were evaluated by a semi-structured clinical interview (SCID-I) in order to ensure diagnostic reliability. This interview model is based on the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision* (DSM-IV-TR), with a translation and adaptation to Portuguese that presents, in general, good reliability, with excellent Kappa coefficient (0.87) for mood disorders³⁰. The interviews were conducted by two Ph.D students, who underwent intensive training under supervision of a senior researcher. After the Bipolar II diagnosis was validated, the subjects were referred to psychiatric services of the public health system. However, due to the difficulty in obtaining medication in the public health system in the city of Pelotas, a 350.000 habitants-city in southern Brazil, *a psychiatrist had to be assigned to the research team and the subjects referred to the psychiatric outpatient clinic of the Health Campus of UCPel*. The medicated subjects that matched the inclusion criteria (ages between 18 and 29 years, a validated clinical diagnosis of Bipolar II according to SCID and have signed the informed consent) were invited to participate in the trial. Those with suicide risk and/or using illegal drugs were not included and were offered treatment at a specialized outpatient facility. The Economic Index was assessed with the *National Economic Index*,³¹ based on the total of material goods and the householders' schooling, among other items. The socio-economic classes are divided into three levels (high, intermediate and low) for the Brazilian population according to the 2000 Demographic Census.

Outcome Measures

The severity of depressive symptoms was measured with the *Hamilton Depression Rating Scale* (HDRS), a 17-item scale that enables the creation of a discrete variable, in which the higher scores correspond to a higher severity of the symptoms. The internal consistency ranges from 0.83 to 0.94. The scale reliability between raters has been consistent in several studies.³² To assess the intensity of manic symptoms we utilized the *Young Mania Rating Scale* (YMRS), a 11-item scale chosen for its high reliability in measuring severity levels of mania and validity coefficient. The Brazilian validated version,³³ which has an even better reliability level than the original, had its internal consistency assessed by Crombach's α , calculated using analysis of variance applied to the eleven items of the scale. From the resulting co-variance matrix, an $\alpha = 0.67$ was obtained for the scale as a whole and an $\alpha = 0.72$ for each standardized item ($P < 0.001$).

The evaluation of the biological rhythm was made using the Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN). This scale was designed to offer a reliable, validated and standardized measure of biological rhythm, with scores clinically understandable for researchers. The 18 items are divided in four specific areas (sleep, activity, social rhythm and eating pattern) that are rated using a 4-point scale: 1 (no difficulty) and 4 (very difficult). The validity and reliability of the Portuguese BRIAN version are described by Giglio et al,³⁴ including information about its factor analysis and how the areas were selected. All the outcome measures were assessed in two different moments: baseline and post-intervention.

Randomization

Participants were randomly divided into two groups using sealed *envelopes*: a group received a short-term psychoeducation model²⁸ and medication (combined intervention) and the other, only medication (standard intervention). The randomization was made by a team member who did not participate in any of the previous stages of the study. Those who administered the intervention were not blind as to the absence or presence of psychoeducation associated with drug intervention. However, blinding of the baseline and post-intervention evaluators was guaranteed (they were always blinded to subject allocation) by changing the team in the two moments of evaluation.

Interventions

Standard intervention: pharmacological treatment with mood stabilizers. The subjects followed the treatment prescribed by psychiatrists (from the public health system or the research team), according to their needs; Combined intervention: Medication and a short-term psychoeducation model adapted from the *Psychoeducation Manual for Bipolar Disorder developed by Colom & Vieta*.²⁸ The model was summarized in a protocol of six individual sessions of one hour each. Generally, the sessions occurred in the following order: the first introduced the therapist to the patient and explained the treatment guidelines, confidentiality issues, the psychoeducation protocol (“What is it” and “What isn’t it”) and the general concepts of BD (“What is mood?”); the second explained the biological nature of BD, mania and hypomania concepts and the social stigma related to the disease in order to modify inadequate understandings and guilt feelings; the third session involved depressive symptoms; the fourth instructed the patient to detect warning signs of recurrence (through the identification of prodromal behaviors) and the benefits of doing so (developing a pre-defined action plan with techniques and resources); the fifth session provided the patient with options of what to do when an episode was detected, emphasizing the importance of adherence to pharmacological treatment and the contact with the psychiatrist; and finally the sixth and last session, which was a summary of everything that was explained in the previous sessions, reinforcing aspects on which the patient had great difficulty. The intervention was carried out by Psychology undergraduates (in *their final year*), who were trained and supervised by a qualified and experienced researcher.

Regarding the pharmacological treatment in both groups, primarily only medication provided by the Brazilian Public Health System were prescribed, in order to facilitate the continuity of treatment after the end of the study. Lithium was the most commonly used medication and were prescribed alone or combined with other drugs such as anticonvulsants, antidepressants, neuroleptics and benzodiazepines, according to the needs of each patient. There were no statistically significant differences between groups for the use of medication, combined or not.

Statistical Analysis

After coding the baseline and post-intervention assessment tools, data were double entered in the Epi-Info 6.04d software with consistency checked using the Validate command. After that, the data were transferred to SPSS 13.0 software for the statistical analyses, and is presented in three tables, where the first one describes the

characteristics of the sample (baseline) between the two intervention groups. The data are presented in absolute and relative frequencies for qualitative variables with chi-square test for difference between groups. Quantitative variables are described as mean and standard deviation, since they were normally distributed in the Gaussian curve. The difference between means was verified by t test. Table 2 shows, by paired t test, the difference between the mean and confidence interval of the difference in symptom scores and biological rhythm of the baseline and post-intervention presented in the whole group, the standard intervention group and combined intervention group. We also present the effect sizes of each of the associations studied.

In Table 3 linear regression was used to verify the difference between the remission scores of depressive and manic symptoms, as well the biological rhythm regulation between the proposed intervention groups. In the same table we can observe the coefficient of linear regression and the confidence interval of 95% both crude and adjusted for economic index. The data shown are referred to the combined intervention, using the standard intervention as reference. For all the statistical tests significant associations were considered in a 95% significance level ($p < 0.05$).

Participants

A total of 282 young adults were tested for inclusion in the trial. Among these, 220 did not meet the criteria and were referred to the Public Health System. The sample at this point consisted of 61 Bipolar II subjects, 29 for standard intervention and 32 for combined intervention. During the study, there were 14 losses to follow-up (3 from standard intervention and 11 from combined intervention). In addition, a patient refused to take part in the psychoeducation and another was excluded from the study due to illicit substance abuse during the psychoeducation period. Therefore, the final sample consisted of 45 individuals (26 for standard intervention and 19 for combined intervention 19) (Figure 01). The participants were recruited between July 2010 and June 2012 and the final evaluations took place from November 2010 to September 2012.

RESULTS

In this sample, the majority of the participants were women, with an average age of 24 years and 12 years of schooling. Randomization was effective and the distribution was homogeneous in all respects, except the economic index, which showed significant difference between groups ($p = 0.041$). Although the groups were similar as to the

presence of symptoms at baseline, the Social domain ($p < 0.001$) and the total score ($p = 0.040$) of the BRIAN scale were different between groups. Other baseline information is described in Table 1.

Regarding the influence of the interventions on mood symptoms, according to the intention-to-treat analysis ($n = 61$), both groups showed remission of depressive symptoms (Standard $p = 0.006$; Combined $p = 0.041$), but none had statistically significant reduction of manic symptoms. Unlike we expected, there was no statistically significant influence of psychoeducation on biological rhythm between both evaluations. Only the standard intervention group showed improvement in the BRIAN domains: Sleep ($p = 0.012$), Activity ($p < 0.001$), Social rhythm ($p = 0.002$) and total score ($p = 0.001$). All significant associations presented effect sizes between moderate and strong (Table 2). There was no difference in depressive symptoms remission among intervention models after the linear regression. On the other hand, there was a tendency of manic symptoms remission in the combined intervention model after adjustment for economic index ($p = 0.061$). However, a strong biological rhythm regulation was found in the standard intervention group (when compared to combined), regardless of the setting (Table 3).

DISCUSSION AND METHODOLOGICAL CONSIDERATIONS

The results showed that, in this sample and time period evaluated, the combined treatment of medication and psychoeducation had no statistically significant impact on the regulation of biological rhythm, when compared to a standard pharmacological treatment. As the hypothesis investigated was not confirmed, despite the methodological precision in which the study was conducted, relevant research questions emerge for future studies. The economic status, for example, which was relevant mainly in the combined intervention group, has a described negative effect on the response to psychoeducational intervention³⁵.

The sample size, a limitation of our study, reflects the struggle in finding bipolar subjects willing to enter in an investigation when it was not part of a service that they already participate. A possibility is that, because those subjects had only few episodes, they were not yet aware of the importance of treatment. Another two limitations of the study should be noted: the lack of control of the medication used in the standard intervention and a need for emphasis on the importance of a life routine of the subjects on the Psychoeducation model. While these limitations may have influenced the study in

some way, we believe, especially in the medication issue, that the success of randomization has dissipated the effects.

The “how” psychoeducation works is worth questioning. In this particular case, where the subjects answered the questionnaires after the intervention, the psychoeducation may have helped them to become more sensitive in detecting warning signs and more self-demanding in their answers, which is common in mania and hypomania,³⁶ and consequently, lower scores were obtained. Also the treatment duration, time period evaluated and number of sessions probably played a key role in the results obtained. If, on one hand, experimental evidence shows that compact models can be effective,³⁷ in contrast, there is a study design similar to ours,³⁵ which confirms that sixteen sessions (more than twice the number used in this study) did not obtain any changes. Maybe it was not because of the number of sessions, but considering psychoeducation characteristics, the effect may happen over time and appears in follow-up evaluations. In this sense, its *longitudinal effectiveness* in prophylaxis has already been proven.³⁸

CONCLUSION

Although the changes in biological rhythm were not statistically significant during the time period evaluated in this study, it is noteworthy that the trajectory of the score shows a tendency of improvement, what may indicate a contribution even though it may take longer than expected. Psychoeducation is an active component of successful psychosocial interventions for BD,³⁹⁻⁴¹ but models need to be studied and adjusted pragmatically. Other strategies must be considered, such as neuropsychological rehabilitation and social skill training, in order to build a more solid treatment combination. Some interventions do not produce the expected results, maybe due to the design chosen (possibly the topics chosen for the PE played a key role here) or to the uncontrolled variables regarding psychotherapy research but, nonetheless, we can say that psychoeducation is not only welcome in the group of psychosocial interventions offered to bipolar subjects, but it is an indispensable tool in the treatment of bipolar disorder.

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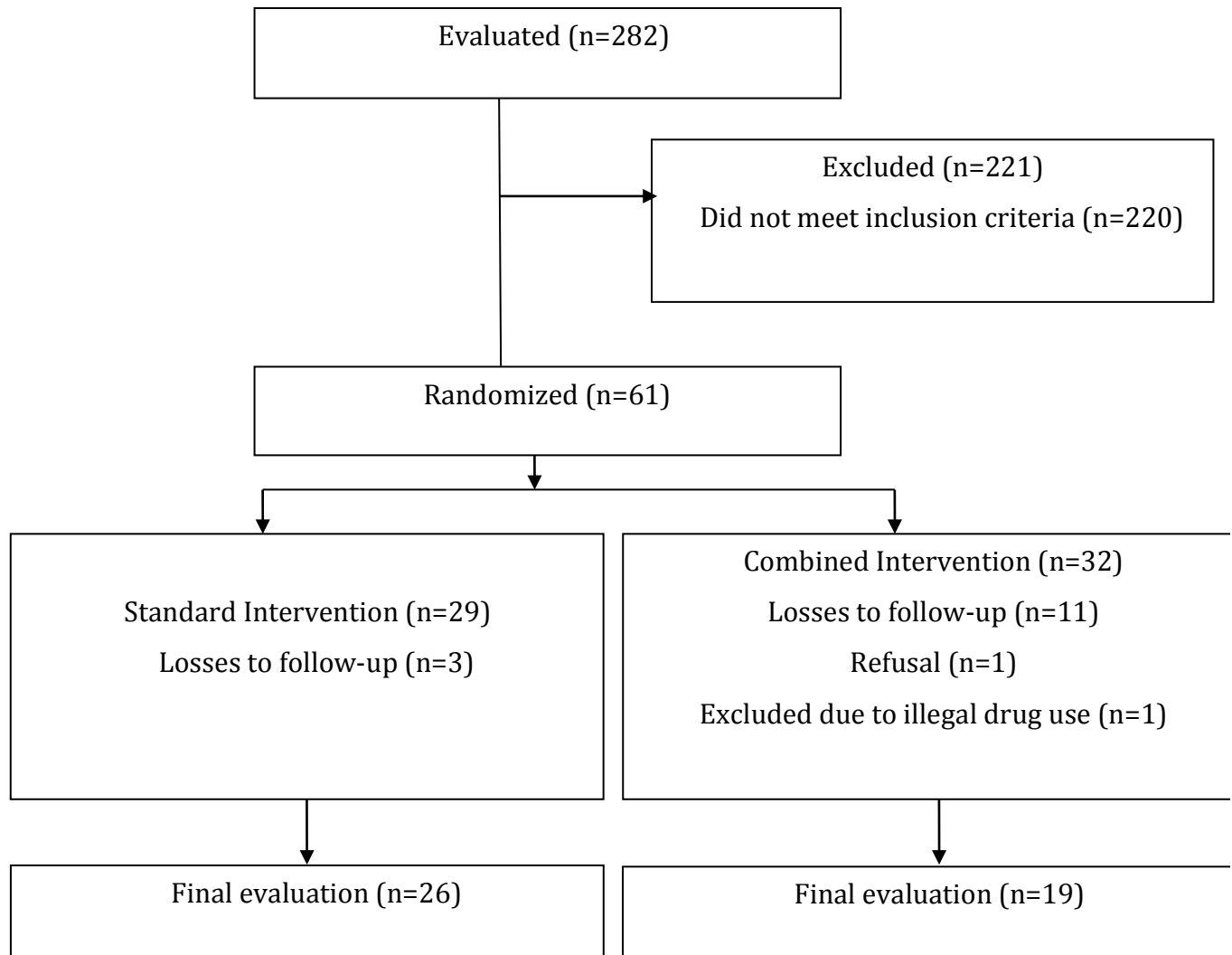
Figure 1 – Participant flow.

Table 1 – Baseline demographic and clinical characteristics of each group.

Demographic and clinical characteristics	Standard intervention n = 29	Combined Intervention n = 32	P-value
Gender			0.768
Female	21 (72.4%)	21 (65.6%)	
Male	8 (27.6%)	11 (34.4%)	
Age (years)	24.03 ($\pm$ 3.57)	24.09 ($\pm$ 3.90)	0.951
Education (years)	12.30 ($\pm$ 3.33)	11.64 ($\pm$ 3.13)	0.467
Economic Index *			0.041
Low	6 (35.3%)	11 (64.7%)	
Intermediate	9 (50.0%)	9 (50.0%)	
High	12 (70.6%)	5 (29.4%)	
Years of illness	5.48 ($\pm$ 4.26)	5.06 ($\pm$ 4.26)	0.702
Current episode			0.466
Euthymic	2 (6.9%)	2 (6.3%)	
Depression	17 (18.6%)	18 (56.3%)	
Hypomania	1 (3.4%)	2 (6.3%)	
Mania	1 (3.4%)	5 (15.6%)	
Mixed	8 (27.6%)	5 (15.6%)	
Depressive symptoms (HDRS)	13.07 ($\pm$ 6.22)	12.22 ($\pm$ 5.96)	0.589
Manic symptoms (YOUNG)	5.83 ($\pm$ 6.58)	7.03 ($\pm$ 8.63)	0.541
Biological Rhythm (BRIAN)	47.43 ($\pm$ 9.46)	44.84 ($\pm$ 11.63)	
Sleep	14.38 ($\pm$ 3.24)	13.81 ($\pm$ 6.45)	0.662
Activity	12.86 ($\pm$ 3.88)	11.16 ($\pm$ 3.62)	0.082
Social rhythm	10.69 ($\pm$ 2.20)	8.56 ($\pm$ 1.81)	<0.001
Eating	11.07 ($\pm$ 2.85)	9.97 ($\pm$ 3.58)	0.193
Total	49.00 ($\pm$ 8.78)	43.50 ($\pm$ 11.55)	0.040

* Missing

Table 2 – Outcome results for each group.

Outcomes	Post-intervention	Differences between means baseline (95% CI)	P-value	Effect-size <i>r</i>
Total sample				
Depression Symptoms	12.57 (±5.79)	2.59 (1.16; 4.02)	0.001*	0.424
Manic symptoms	5.11 (±5.18)	1.34 (-0.72; 3.41)	0.198	0.167
Biological Rhythm				
Sleep	12.82 (±3.58)	1.26 (-0.17; 2.70)	0.083	0.222
Activity	9.87 (±3.36)	2.10 (0.82; 3.38)	0.002*	0.390
Social rhythm	8.82 (±2.58)	0.75 (-0.04; 1.54)	0.061	0.239
Eating	9.66 (±3.57)	0.84 (-0.31; 1.98)	0.150	0.185
Total	41.16 (±9.17)	4.95 (1.24; 8.66)	0.010*	0.326
Standard intervention (n=29)				
Depression symptoms	12.62 (±5.49)	3.55 (1.09; 6.01)	0.006*	0.487
Manic symptoms	5.62 (±4.40)	0.21 (-2.88; 3.30)	0.892	0.026
Biological Rhythm				
Sleep	12.17 (±3.62)	2.21 (0.52; 3.89)	0.012*	0.451
Activity	9.41 (±3.41)	3.45 (1.66; 5.23)	<0.001*	0.599
Social rhythm	8.62 (±2.87)	2.07 (0.84; 3.30)	0.002*	0.545
Eating	9.62 (±3.71)	1.45 (-0.15; 3.05)	0.074	0.331
Total	39.83 (±9.18)	9.17 (4.04; 14.31)	0.001*	0.569
Combined intervention (n=32)				
Depression symptoms	12.53 (±6.14)	1.72 (0.07; 3.36)	0.041*	0.357
Manic symptoms	4.66 (±5.82)	2.37 (-0.50; 5.25)	0.102	0.289
Biological Rhythm				
Sleep	13.41 (±3.49)	0.41 (-1.91; 2.72)	0.723	0.064
Activity	10.28 (±3.31)	0.87 (-0.93; 2.68)	0.330	0.175
Social rhythm	9.00 (±2.33)	-0.44 (-1.31; 0.44)	0.315	0.180
Eating	9.69 (±3.49)	0.28 (-1.41; 1.98)	0.738	0.060
Total	42.38 (±9.14)	1.12 (-4.10; 6.35)	0.664	0.079

Table 3 – Crude and adjusted linear regression for symptoms remission and biological rhythm regulation comparisons between intervention groups.

Outcomes	Crude		Adjusted for economic index	
	B (95% CI)	P-value	B (95% CI)	P-value
Depression symptom remission				
<i>Combined intervention</i>	-1.07 (-4.91; 2.77)	0.578	-1.86 (-6.34; 2.61)	0.404
Manic symptom remission				
<i>Combined intervention</i>	3.78 (-1.88; 9.42)	0.185	5.93 (-0.28; -12.15)	0.061
Biological Rhythm regulation				
<i>Combined intervention</i>	-10.89 (-18.84; -2.95)	0.008	-10.84 (-20.61; -1.07)	0.031

CONSIDERAÇÕES FINAIS

Ao longo deste trabalho buscou-se, inicialmente, apresentar um projeto de pesquisa com diferentes delineamentos aninhados, um estudo transversal com amostra comunitária serviu de base para a seleção dos sujeitos que compuseram o caso-controle com os sujeitos positivos para transtornos de humor e controles populacionais pareados, além disso, os jovens com diagnóstico de transtorno bipolar foram convidados a participar de um ensaio clínico randomizado.

Cumpridas as etapas de elaboração e execução do projeto, procedeu-se a análise dos dados e confecção dos dois artigos que vieram a compor a tese. Cabe aqui apontar as conclusões destes artigos, que de forma geral tinham como objetivo primário a avaliação do prejuízo no ritmo biológico em sujeitos com Transtorno Bipolar e a verificação da influência de um modelo de psicoeducação na regulação do ritmo biológico. A fim de facilitar a compreensão dos achados, os principais resultados dos dois artigos são apresentados a seguir:

1º ARTIGO – Biological rhythm disruption in Bipolar Disorder: a case-control study in a population-based sample of young adults

Objetivo: Avaliar a regulação do Ritmo Biológico em indivíduos com transtorno bipolar de uma amostra de base populacional de jovens adultos, em comparação com dois grupos controle: no primeiro, sujeitos sem histórico prévio de transtornos do humor; no segundo, indivíduos diagnosticados com depressão unipolar.

- Os escores da BRIAN foram maiores em sujeitos com Transtorno Bipolar em episódio atual quando comparados aos controles e sujeitos com deprimidos em remissão.
- Além disso, encontramos escores da BRIAN aumentados em sujeitos deprimidos em episódios atuais e bipolares em remissão quando comparados a controles saudáveis.
- Sintomas depressivos apresentaram uma correlação positiva com alteração no ritmo biológico em sujeitos com depressão e transtorno bipolar.

2º ARTIGO – *The influence of Psychoeducation on regulating biological rhythm in a sample of patients with bipolar disorder: a randomized clinical trial*

Objetivo: Comparar dois modelos de intervenção para pacientes bipolares: uma intervenção padrão, medicamentosa, e uma intervenção combinada, de medicação e um modelo breve e manualizado de Psicoeducação.

- Ambos os grupos apresentaram remissão dos sintomas depressivos, mas nenhuma redução estatisticamente significativa nos sintomas maníacos.
- Ao contrário do esperado, não houve influência estatisticamente significativa da psicoeducação no ritmo biológico em ambas as avaliações.
- Apenas o grupo da intervenção padrão apresentou melhoras nos domínios da BRIAN: sono, ritmo social, atividade e escore total.
- Na comparação com a intervenção combinada (medicação + psicoeducação) o grupo da intervenção padrão apresentou forte regulação do ritmo biológico.

Os resultados não confirmaram a hipótese, mostrando que, nessa amostra, o tratamento combinado de medicação e psicoeducação não teve impacto significativo na regulação do ritmo biológico quando comparado ao tratamento farmacológico padrão.

Por fim, é importante salientar que o método científico não é capaz de abarcar a realidade da vida humana e, ao contrário, ao buscar-se controlar as variáveis envolvidas é inevitável a criação de situações que se distanciam do cotidiano das pessoas. Assim, este trabalho, com suas virtudes e limitações, buscou apresentar um ritmo funcional como um construto viável dentro do campo de estudo dos transtornos do humor e, mais especificamente, do transtorno bipolar.

ANEXOS

ANEXO 1 – *Hamilton Depression Rating Scale* (HDRS)

1. HUMOR DEPRIMIDO (Tristeza, desesperança, desamparo, inutilidade)

- (0) Ausente
- (1) Sentimentos relatados apenas ao ser inquirido
- (2) Sentimentos relatados espontaneamente com palavras
- (3) Comunica os sentimentos não com palavras, isto é, com a expressão facial, a postura, a voz e a tendência ao choro.
- (4) Sentimentos deduzidos da comunicação verbal e não-verbal do paciente

2. SENTIMENTOS DE CULPA

- (0) Ausente
- (1) Auto-recriminação; sente que decepcionou os outros
- (2) Ideias de culpa ou ruminação sobre erros passados ou más ações
- (3) A doença atual é um castigo
- (4) Ouve vozes de acusação ou denúncia e/ou tem alucinações visuais ameaçadoras

3. SUICÍDIO

- (0) Ausente
- (1) Sente que a vida não vale a pena
- (2) Desejaria estar morto ou pensa na probabilidade de sua própria morte
- (3) Ideias ou gestos suicidas
- (4) Tentativa de suicídio (qualquer tentativa séria, marcar 4)

4. INSÔNIA INICIAL

- (0) Sem dificuldades para conciliar o sono
- (1) Queixa-se de dificuldade ocasional para conciliar o sono, isto é, mais de meia hora
- (2) Queixa-se de dificuldade para conciliar o sono todas as noites

5. INSÔNIA INTERMEDIÁRIA

- (0) Sem dificuldades
- (1) O paciente se queixa de inquietude e perturbação durante a noite
- (2) Acorda à noite - qualquer saída da cama marcar 2 (exceto p/ urinar)

6. INSÔNIA TARDIA

- (0) Sem dificuldades

- (1) Acorda de madrugada, mas volta a dormir
- (2) Incapaz de voltar a conciliar o sono se deixar a cama

7. TRABALHO E ATIVIDADES

- (0) Sem dificuldades
- (1) Pensamento e sentimentos de incapacidade, fadiga ou fraqueza relacionada a atividades, trabalho ou passatempos
- (2) Perda de interesse por atividades (passatempos ou trabalho) quer diretamente relatada pelo paciente, quer indiretamente por desatenção, indecisão e vacilação (sente que precisa esforçar-se para o trabalho ou atividade)
- (3) Diminuição do tempo gasto em atividades ou queda de produtividade. No hospital, marcar 3 se o paciente não passar ao menos 3 horas por dia em atividades externas (trabalho hospitalar ou passatempo)
- (4) Parou de trabalhar devido à doença atual. No hospital, marcar 4 se o paciente não se ocupar com outras atividades, além de pequenas tarefas do leito, ou for incapaz de realizá-las sem ajuda

8. RETARDO *(lentidão de idéias e fala; dificuldade de concentração; atividade motora diminuída)*

- (0) Pensamento e fala normal
- (1) Leve retardo à entrevista
- (2) Retardo óbvio à entrevista
- (3) Entrevista difícil
- (4) Estupor completo

9. AGITAÇÃO

- (0) Nenhuma
- (1) Inquietude
- (2) Brinca com as mãos, com os cabelos, etc
- (3) Mexe-se, não consegue sentar quieto
- (4) Torce as mãos, rói as unhas, puxa os cabelos, morde os lábios

10. ANSIEDADE PSÍQUICA

- (0) Sem dificuldade
- (1) Tensão e irritabilidade subjetivas
- (2) Preocupação com trivialidades

- (3) Atitude apreensiva aparente no rosto ou na fala
- (4) Medos expressos sem serem inquiridos

11. ANSIEDADE SOMÁTICA - *Concomitantes fisiológicos de ansiedade, tais como:*

- *Gastrointestinais: boca seca, flatulência, indigestão, diarreia, cólicas, eructação;*
- *Cardiovasculares: palpitações, cefaléia;*
- *Respiratórios: hiperventilação, suspiros; Frequência urinária; Sudorese*

- (0) Ausente
- (1) Leve
- (2) Moderada
- (3) Grave
- (4) Incapacitante

12. SINTOMAS SOMÁTICOS GASTRINTESTINAIS

- (0) Nenhum
- (1) Perda de apetite, mas alimenta-se voluntariamente. Sensações de peso no abdômen
- (2) Dificuldade de comer se não insistirem. Solicita ou exige laxativos ou medicações para os intestinos ou para sintomas digestivos

13. SINTOMAS SOMÁTICOS EM GERAL

- (0) Nenhum
- (1) Peso nos membros, nas costas ou na cabeça. Dores nas costas, cefaléia, mialgias. Perda de energia e cansaço
- (2) Qualquer sintoma bem caracterizado e nítido (marcar 2)

14. SINTOMAS GENITAIS (*Sintomas como: perda da libido, distúrbios menstruais*)

- (0) Ausentes
- (1) Leves
- (2) Intensos

15. HIPOCONDRIA

- (0) Ausente
- (1) Auto-observação aumentada (com relação ao corpo)
- (2) Preocupação com a saúde
- (3) Queixas freqüentes, pedidos de ajuda, etc
- (4) Idéias delirantes hipocondríacas

16. PERDA DE PESO (Marcar A ou B)

- A - Quando avaliada pela história clínica

- (0) Sem perda de peso
- (1) Provável perda de peso associada à moléstia atual
- (2) Perda de peso definida (de acordo com o paciente)
- (3) Não avaliada

- B - Avaliada semanalmente pelo psiquiatra responsável, quando são medidas alterações reais de peso

- (0) Menos de 0,5 Kg de perda por semana
- (1) Mais de 0,5 Kg de perda por semana
- (2) Mais de 1 Kg de perda por semana
- (3) Não avaliada

17. CONSCIÊNCIA

- (0) Reconhece que está deprimido e doente
- (1) Reconhece a doença, mas atribui-lhe a causa à má alimentação, ao clima, ao excesso de trabalho, a vírus, à necessidade de repouso, etc
- (2) Nega estar doente
- (8) Não está doente

ANEXO 2 – *Young Mania Rating Scale* (YMRS)

01. HUMOR E AFETO ELEVADOS

- (0) Ausência de elevação do humor ou afeto
- (1) Humor ou afeto discretos ou possivelmente aumentados, quando questionado
- (2) Relato subjetivo de elevação clara do humor; mostra-se otimista, autoconfiante, alegre; afeto apropriado ao conteúdo do pensamento
- (3) Afeto elevado ou inadequado ao conteúdo do pensamento; jocoso
- (4) Eufórico; risos inadequados, cantando

02. ATIVIDADE MOTORA - ENERGIA AUMENTADA

- (0) Ausente
- (1) Relato subjetivo de aumento da energia ou atividade motora
- (2) Apresenta-se animado ou com gestos aumentados
- (3) Energia excessiva; às vezes hiperativo; inquieto (mas pode ser acalmado)
- (4) Excitação motora; hiperatividade contínua (não pode ser acalmado)

03. INTERESSE SEXUAL

- (0) Normal; sem aumento
- (1) Discreta ou possivelmente aumentado
- (2) Descreve aumento subjetivo, quando questionado
- (3) Conteúdo sexual espontâneo; discurso centrado em questões sexuais; auto-relato de hipersexualidade
- (4) Relato confirmado ou observação direta de comportamento explicitamente sexualizado, pelo entrevistador ou outras pessoas

04. SONO

- (0) Não relata diminuição do sono
- (1) Dorme menos que a quantidade normal, cerca de 1 hora a menos do que o seu habitual.
- (2) Dorme menos que a quantidade normal, mais que 1 hora a menos do que o seu habitual.
- (3) Relata diminuição da necessidade de sono
- (4) Nega necessidade de sono

05. IRRITABILIDADE

- (0) Ausente
- (2) Subjetivamente aumentada

- (4) Irritável em alguns momentos durante a entrevista; episódios recentes (nas últimas 24 horas) de ira ou irritação na enfermaria
- (6) Irritável durante a maior parte da entrevista; ríspido e lacônico o tempo todo
- (8) Hostil; não cooperativo; entrevista impossível

06. FALA (VELOCIDADE E QUANTIDADE)

- (0) Sem aumento
- (2) Percebe-se mais falante do que o seu habitual
- (4) Aumento da velocidade ou quantidade da fala em alguns momentos; verborréico, às vezes (com solicitação, consegue-se interromper a fala)
- (6) Quantidade e velocidade constantemente aumentadas; dificuldade para ser interrompido (não atende a solicitações; fala junto com o entrevistador)
- (8) Fala pressionada, ininterruptível, contínua (ignora a solicitação do entrevistador)

07. LINGUAGEM – DISTÚRPIO DO PENSAMENTO

- (0) Sem alterações
- (1) Circunstancial; pensamentos rápidos
- (2) Perde objetivos do pensamento; muda de assuntos freqüentemente; pensamentos muito acelerados
- (3) Fuga de idéias; tangencialidade; dificuldade para acompanhar o pensamento; ecolalia consonante
- (4) Incoerência; comunicação impossível

08. CONTEÚDO

- (0) Normal
- (2) Novos interesses e planos compatíveis com a condição sócio-cultural do paciente, mas questionáveis
- (4) Projetos especiais totalmente incompatíveis com a condição sócio-econômica do paciente; hiper-religioso
- (6) Idéias supervalorizadas
- (8) Delírios

09. COMPORTAMENTO DISRUPTIVO AGRESSIVO

- (0) Ausente, cooperativo
- (2) Sarcástico; barulhento, às vezes, desconfiado
- (4) Ameaça o entrevistador; gritando; entrevista dificultada

(6) Agressivo; destrutivo; entrevista impossível

10. APARÊNCIA

(0) Arrumado e vestido apropriadamente

(1) Descuidado minimamente; adornos ou roupas minimamente inadequados ou exagerados

(2) Precariamente asseado; despenteado moderadamente; vestido com exagero

(3) Desgrenhado; vestido parcialmente; maquiagem extravagante

(4) Completamente descuidado; com muitos adornos e adereços; roupas bizarras

11. INSIGHT (DISCERNIMENTO)

(0) Insight presente: espontaneamente refere estar doente e concorda com a necessidade de tratamento

(1) Insight duvidoso: com argumentação, admite possível doença e necessidade de tratamento

(2) Insight prejudicado: espontaneamente admite alteração comportamental, mas não a relaciona com a doença, ou discorda da necessidade de tratamento

(3) Insight ausente: com argumentação, admite de forma vaga alteração comportamental, mas não a relaciona com a doença e discorda da necessidade de tratamento

(4) Insight ausente: nega a doença, qualquer alteração comportamental e necessidade de tratamento

ANEXO 3 – *Biological Rhythm Interview of Assessment in Neuropsychiatry* (BRIAN)

Dos aspectos indicados abaixo assinale a opção que melhor descreve a conduta do paciente nos **últimos 15 dias**.

(1) nenhuma

(2) pouca

(3) bastante

(4) muita

SONO

1. Qual o seu grau de dificuldade em dormir na hora habitual .
2. Qual o seu grau de dificuldade em acordar na hora habitual.
3. Qual o seu grau de dificuldade em sair da cama depois de despertar.
4. Qual o seu grau de dificuldade em sentir-se descansado com o número de horas que dorme (estar descansado inclui a sensação subjetiva e desempenho normal em tarefas diárias como dirigir, raciocinar e trabalhar).
5. Qual o seu grau de dificuldade em “desligar” nos momentos de descanso?

ATIVIDADES

6. Qual o seu grau de dificuldade em terminar todas as atividades que faz em seu trabalho?
7. Qual o seu grau de dificuldade em terminar suas atividades habituais (limpar a casa, fazer compras)?
8. Qual o seu grau de dificuldade em manter seu ritmo de atividade física (por exemplo: tomar um ônibus/metro ou praticar um esporte – se isto faz parte de sua rotina)
9. Qual é seu grau de dificuldade em cumprir o horário habitual de suas tarefas.
10. Qual o seu grau de dificuldade em manter seu nível de desejo/atividade sexual?

SOCIAL

11. Qual o seu grau de dificuldade em relacionar-se e comunicar-se com as pessoas com quem convive?
12. Qual o seu grau de dificuldade em usar de forma equilibrada aparelhos eletrônicos como TV, internet, etc. (sem que isto prejudique seu contato com as pessoas com quem convive ou gastem um número de horas desproporcionais as seus outros afazeres).
13. Qual o grau de dificuldade em ajustar suas rotinas e padrão de sono ao das pessoas com quem convive (familiares, vizinhos, amigos).
14. Qual o grau de dificuldade em disponibilizar de tempo e atenção para as pessoas com quem convive (familiares, vizinhos, amigos)?

ALIMENTAÇÃO

15. Qual o seu grau de dificuldade em manter o horário das suas refeições (café da manhã, almoço e jantar)?
16. Qual o seu grau de dificuldade em manter seu padrão alimentar habitual no que se refere a não pular refeições?
17. Qual o seu grau de dificuldade em manter seu padrão alimentar habitual no que se refere a quantidade de alimento ingerido?
18. Qual o seu grau de dificuldade em consumir com moderação estimulantes (como café e coca-cola) ou chocolates/doces?

RITMO PREDOMINANTE (vespertino ou matutino)

Esta parte da escala é opcional e se refere aos seus hábitos. Considere aqui os últimos 12 meses.

(1) nunca (2) raramente (3) quase sempre (4) sempre

19. Você tem a tendência a estar mais ativo à noite (trabalho, relações interpessoais)?
20. Você tem a sensação que pela manhã é mais produtivo?
- 21- Você tem trocado seu dia pela noite?