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**A INFLUÊNCIA DA RELIGIOSIDADE
NOS TRANSTORNOS MENTAIS**

TESE DE DOUTORADO

Salvador
2015

ANDRÉ CARVALHO CARIBÉ DE ARAÚJO PINHO

**A INFLUÊNCIA DA RELIGIOSIDADE
NOS TRANSTORNOS MENTAIS**

Tese apresentada ao Programa de Pós-graduação em Medicina e Saúde, da Faculdade de Medicina da Bahia, Universidade Federal da Bahia, como requisito para a obtenção do grau de Doutor em Medicina e Saúde

Orientadora: Profa. Dra. Ângela Miranda Scippa.

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RESUMO

Objetivo: Estudar as relações entre a religiosidade e suas principais dimensões nos transtornos psiquiátricos e no comportamento suicida (CS). **Métodos:** 1- Revisão clássica da literatura sobre religiosidade/espiritualidade em pacientes com transtornos de humor e com comportamento suicida. 2- Estudo de corte transversal que avalia as relações entre a religiosidade e a impulsividade, comparando portadores de transtorno mental que tentaram suicídio com controles saudáveis. 3- Estudo de corte transversal multicêntrico que investiga a relação entre religiosidade e CS em pacientes bipolares tipo I. 4-Relato de caso de uma síndrome psicótica com conteúdo religioso. **Resultados:** 1- A presença de religiosidade está associada a melhores desfechos em saúde mental. 2-Controles saudáveis apresentam maiores níveis de religiosidade e menor impulsividade quando comparados a pacientes com doença mental. Nestes pacientes, a religiosidade intrínseca (RI) apresentou relação inversa com: impulsividade total ($p= 0.023$), atencional ($p=0.010$) e ausência de planejamento ($p= 0.07$). 3- Nos pacientes bipolares, maior religiosidade não organizacional (RNO) (OR, 0.66; 95% CI, 0.50 - 0.86) e maior RI (OR, 0.70; 95% CI, 0.60 - 0.81) se associaram a menor CS nesta população. 4- Psicose lúpica se manifestou com sintomas de conteúdo religioso que culminou com homicídio. **Conclusões:** A religiosidade apresenta uma relação inversa com impulsividade e a presença de doença mental pode interferir nesta relação. A religiosidade se mostrou como fator protetor ao CS em pacientes com TB tipo I. Sintomas religiosos podem fazer parte do conteúdo das psicoses e interferir no seu desfecho.

Palavras-chave: religiosidade, espiritualidade, impulsividade, comportamento suicida, transtorno bipolar, transtorno afetivo, tentativa de suicídio, suicídio.

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ABSTRACT

Objective: Study the relations between religiosity and its main dimensions with mental health outcomes in diverse populations, with emphasis on mood disorders and suicidal behavior (SB). **Methods:** 1- Classic review of the literature on religiosity/spirituality in patients with mood disorders and suicidal behavior. 2- Cross-sectional study evaluating the relations between religiosity and impulsivity, comparing healthy controls to mental disorder patients who attempted suicide. 3- Case report of a patient with a psychotic syndrome of mystical/religious character. 4- Multicenter, cross-sectional study investigating the relation between religiosity and SB in type 1 bipolar patients. **Results:** 1- The presence of religiosity is associated with better outcomes in mental health. 2- Healthy controls presented higher levels of religiosity and less impulsivity when compared to mental disorder patients. Regarding these patients, intrinsic religiosity (IR) presented an inverse relation with: total impulsivity ($p= 0.023$), attention ($p=0.010$) and lack of planning ($p= 0.07$). 3- Lupus psychosis generated mystical religious symptoms that culminated in a homicide. 4- In bipolar patients, higher non-organizational religiosity (NOR) (OR, 0.66; 95% CI, 0.50 - 0.86) and intrinsic religiosity (IR) (OR, 0.70; 95% CI, 0.60 - 0.81) were associated with less SB in this population. **Conclusions:** Religious involvement presents an inverse relation to impulsivity and the presence of mental illness may interfere in this relation. Religiosity was shown to be a protective factor against suicidal behavior in type 1 bipolar patients. Mystical and religious symptoms can be present in psychosis.

Keywords: religiosity, spirituality, impulsivity, suicidal behavior, bipolar disorder, affective disorder, suicide attempt, suicide.

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LISTA DE ABREVIATURAS E SIGLAS

AI	<i>Attentional Impulsiveness</i>
ANA	<i>Antinuclear Antibody</i>
AP	<i>Absence of Planning</i>
BD	<i>Bipolar Disorder</i>
BIS 11	<i>Barratt Impulsiveness Scale</i>
CETHA	<i>Program of mood and anxiety disorders</i>
CI	<i>Confidence intervals</i>
CIAVE	<i>Anti-poison information center</i>
DRI	<i>Duke Religious Index-DUREL</i>
DSM-IV	Manual Diagnóstico e Estatístico de Transtornos Mentais, quarta edição
DUREL	<i>Duke University Religion Index</i>
GAD	<i>Generalized Anxiety Disorder</i>
HDRS	<i>Hamilton Depression Rating Scale</i>
HRI	<i>High Religious Involvement</i>
IR	<i>Intrinsic Religiosity</i>
LRI	<i>Low Religious Involvement</i>
MD	<i>Major Depression</i>
MI	<i>Motor Impulsiveness</i>
M.I.N.I.PLUS	<i>Mini International Neuropsychiatric Inter-view</i>
NON-SA	<i>Non-suicide Attempters</i>
NOR	<i>Non-organizational Religiosity</i>
NORA	<i>Non-organizational Religious Activities</i>
OR	<i>Organizational Religiosity</i>
ORA	<i>Organizational Religious Activities</i>
PET-SCAN	<i>Positron Emission Tomography</i>
QoL	<i>Quality of life</i>
SA	<i>Suicide Attempt</i>
SB	<i>Suicidal Behavior</i>
SLE	<i>Systemic Lupus Erythematosus</i>
TI	<i>Total Impulsivity</i>
YMRS	<i>Young Mania Rating Scale</i>

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1 INTRODUÇÃO

A relação entre a religiosidade/espiritualidade (R/E) e a doença mental sempre intrigou a comunidade científica e leigos. Desde a Antiguidade, espiritualidade e saúde estiveram intimamente relacionadas, porém no final do século XIX, a ciência se distanciou da religião, diante da necessidade de se firmar como conhecimento autônomo. Desde então, construiu-se a ideia de que religião, saúde e psiquiatria estiveram em conflito, pensamento que, de certa forma, ainda é prevalente. Este suposto conflito entre R/E e saúde mental se consolidou de diversas formas, principalmente nos países ocidentais, devido à postura de alguns intelectuais influentes dos séculos IX e XX, tais como Charcot, Freud e Henry Maudsley que acreditavam que as experiências religiosas estavam associadas a menor desenvolvimento social e intelectual e seriam manifestação de quadros psicopatológicos.

Apenas nas últimas décadas, pesquisas científicas têm demonstrado que o envolvimento religioso, além de, na maioria das vezes, não ser patológico, evidencia uma associação positiva com saúde mental e bem-estar. No que se refere às doenças mentais, a espiritualidade, geralmente, atua como mecanismo de proteção e ferramenta de enfrentamento em relação ao curso da patologia. Em algumas situações, porém, a R/E e as circunstâncias culturais que as envolvem podem interferir na apresentação psicopatológica, dificultando ou impedindo o diagnóstico e o tratamento médico adequados.

Embora a existência de ligações entre religiosidade e saúde tenham sido estabelecidas, pouco se sabe sobre como os vários aspectos do envolvimento religioso traduz-se em resultados em saúde. Muitos mecanismos têm sido propostos para explicar essas relações, como por exemplo: menos comportamento de risco, mais suporte social, maior enfrentamento positivo, mais senso de significado da vida, esperança, afeto positivo, compaixão e senso de controle.

Entretanto, a quase totalidade dos estudos publicados, até o momento, sobre R/E e comportamento suicida (CS) foram realizados na Europa e na América do Norte. Além disso, muitos deles não estabeleceram controle adequado de variáveis confundidoras, tais como tipo de doença mental associada ao CS, ter filhos ou não, dentre outras. Em relação ao transtorno bipolar (TB) especificamente, não houve um

controle adequado do estado de eutimia dos pacientes, nem do subtipo de doença bipolar e também não se mediu concomitante o nível de impulsividade. Assim, o objetivo deste trabalho é estudar as relações que se estabelecem entre a religiosidade e suas principais dimensões nos transtornos psiquiátricos, com ênfase nos transtornos de humor e no CS.

A ideia de estudar a R/E começou com a curiosidade de observar as influências da vivência religiosa no comportamento humano. De fato, as práticas religiosas acompanham a evolução da humanidade de uma forma transcultural, apesar de todo o desenvolvimento tecnológico e científico, a R/E se mantém como algo importante para a maioria das pessoas.

Em 2011, desenvolvemos o primeiro estudo no Brasil sobre a influência da religiosidade no CS de indivíduos que tentaram suicídio com o uso de substâncias tóxicas atendidos em serviço de emergência de um Centro Antiveneno. Nele, verificamos que mesmo após o controle adequado de variáveis confundidoras, a R/E se mostrou como importante fator de proteção em relação ao CS.

Neste Doutorado, dando continuidade a essa linha de pesquisa investigamos a religiosidade como provável modificador da impulsividade em pacientes com e sem doença mental. Além disso, demonstramos que a religiosidade não organizacional e a intrínseca exercem efeito de proteção sobre o CS em pacientes com TB avaliados em eutimia. Relatamos também um caso clínico, no qual as vivências religiosas e culturais de uma família se misturam com as manifestações psicopatológicas em um quadro de psicose lúpica.

Dessa forma, esperamos que este trabalho contribua para a expansão desta linha de pesquisa, a fim de que possamos entender melhor as complexas relações entre R/E e doença mental, nos seus diversos aspectos.

2 OBJETIVOS

2.1 RELIGIOSITY AND IMPULSIVITY IN MENTAL HEALTH: IS THERE A RELATIONSHIP?

Geral:

Comparar a relação entre religiosidade e impulsividade em pacientes com doença mental que tentaram suicídio com indivíduos saudáveis.

Específico:

Descrever as dimensões da religiosidade e da impulsividade em pacientes com doença mental e controles saudáveis.

2.2 IS RELIGIOSITY A PROTECTIVE FACTOR AGAINST SUICIDAL BEHAVIOR IN BIPOLAR I OUTPATIENTS?

Geral:

Avaliar se há associação entre religiosidade e comportamento suicida em pacientes com transtorno bipolar tipo I avaliados em estado de eutímia.

Específico: Comparar o nível de religiosidade e impulsividade entre pacientes bipolares com e sem história de TS.

2.3 SYSTEMIC LUPUS, FOLIE A TROIS AND HOMICIDE

Relatar um caso clínico de uma paciente com psicose lúpica e *folie a trois*, discorrendo sobre sintomas psicóticos e seus limites com crenças religiosas e culturais.

3 ARTIGO DE REVISÃO

3.1 RELIGIOSIDADE E DOENÇA MENTAL: QUAL A RELAÇÃO ENTRE ELAS NOS TRANSTORNOS DE HUMOR E NO COMPORTAMENTO SUICIDA?

Em revisão

Religiosidade e doença mental: Qual a relação entre elas nos transtornos de humor e no comportamento suicida?

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Resumo

Nas últimas décadas pesquisas vem sendo realizadas com o intuito de compreender as complexas relações entre religiosidade, espiritualidade (R/E) e saúde mental, investigando o papel delas no prognóstico de várias doenças mentais. O objetivo deste trabalho é realizar uma revisão clássica da literatura sobre as relações entre R/E, transtornos de humor e comportamento suicida. O Método utilizado foi uma pesquisa bibliográfica em bases de dados que incluem *Medline*, *Scielo* e *Lilacs*. Para a seleção dos estudos, foi adotado como critério de inclusão artigos sobre e R/E com desfechos clínicos em depressão, transtorno bipolar e comportamento suicida, publicados em inglês ou português, no período de 2010 a 2015. As palavras-chave pesquisadas foram: *religiosity*, *spirituality* e seus cruzamentos com *bipolar disorder*, *affective disorder*, *depression*, *suicide*, *suicide attempt*, *suicidal behavior*, and *suicidality*. A maioria dos estudos selecionados mostrou uma relação significativa entre maiores níveis de religiosidade e melhores desfechos clínicos e psicopatológicos. Apesar dos avanços na compreensão da relação entre R/E e saúde mental, mais pesquisas são necessárias, no intuito de identificar quais os elementos específicos da religiosidade medeiam esta relação e, como, futuramente, esses conhecimentos poderão ser aplicados na prática clínica.

Palavras-chave: Religiosidade, Espiritualidade, Transtorno Bipolar, Transtorno Afetivo, Depressão, Suicídio, Tentativa de Suicídio, Comportamento Suicida.

Abstract

In the last decades, research has been carried out in order to understand the complex relations between religiosity, spirituality (R/S) and mental health, and to investigate the role of R/S in the prognosis of several mental disorders. The objective of this work is to carry out a classic review of the literature on the relations between R/S, mood disorders and suicidal behavior. The method used was bibliographical research in databases that included Medline, Scielo and Lilacs. For the study selection, the inclusion criteria adopted were articles about R/S with clinical outcomes in depression, bipolar disorder and suicidal behavior, published in English or Portuguese, between 2010 and 2015. Key Words: religiosity, spirituality and their cross-links to bipolar disorder, affective disorder, depression, suicide, suicide attempt, suicidal behavior, and suicidality. Most of the selected studies showed a significant relation between higher levels of religious participation and better clinical and psychopathological outcomes. Despite advances made in comprehending the relation between R/S and mental health, more research is necessary, in order to identify which specific elements of religiosity mediate this relation, and how, in the future, to apply this knowledge in clinical practice.

Key Words: Religiosity, Spirituality, Suicidal Behavior, Bipolar Disorder, Affective Disorder, Suicide Attempt, Suicide.

Introdução

A relação entre religiosidade/espiritualidade (R/E) e doença mental sempre esteve presente na história da humanidade. De fato, religiosos vem se ocupando dos cuidados a pessoas enfermas da idade média até os dias atuais (STROPPA e MOREIRA ALMEIDA, 2009). Contudo, no final do século XIX, a ciência se distanciou da religião, diante da necessidade de se firmar como conhecimento autônomo. Naquele período, construiu-se a ideia de que as relações entre a religião, a saúde mental e a psiquiatria seriam conflitantes (KOENIG et al., 2001), mito que de certa forma, ainda persiste na atualidade (MOREIRA-ALMEIDA, 2006).

O suposto conflito entre R/E saúde mental se consolidou de diversas formas, principalmente nos países ocidentais, devido à postura de alguns intelectuais influentes dos séculos XIX e XX, tais como Charcot, Sigmund Freud e Henry Maudsley que acreditavam que as experiências religiosas estavam associadas a menor desenvolvimento social, intelectual e seriam manifestação de quadros psicopatológicos (FREUD, 1962; MOREIRA-ALMEIDA et al., 2005). Ainda no final dos anos de 1980, o psicólogo Albert Ellis, fundador da terapia racional emotiva, apontava a religiosidade como equivalente ao pensamento irracional e ao distúrbio emocional. Ele defendia a ideia de que a solução adequada para problemas emocionais era não ser religioso, pois quanto menos religiosas as pessoas fossem, mas emocionalmente estáveis elas seriam (KOENIG, 2012). Essas afirmações, de certa forma, influenciaram o pensamento da época e foram adotadas no Manual Diagnóstico e Estatístico de Transtornos Mentais-DSM-III-R (APA, 1983) que utilizou descrições com conteúdos religiosos para exemplificar quadros psicopatológicos (LARSON et al., 1993).

Apenas nas últimas décadas, trabalhos científicos realizados nas áreas médica e psicológica demonstraram que o envolvimento religioso, além de não ser, necessariamente, patológico tem uma associação positiva com saúde mental e bem estar (KOENIG, 2009). De fato, o nível de envolvimento religioso tende a ser inversamente relacionado à depressão, ao comportamento suicida (CS), ao uso de drogas, a impulsividade e ao jogo patológico (CASEY et al, 2011; CARIBÉ et al., 2012; RONNEBERG et al., 2014). Porém, nem sempre a vivência religiosa se traduz em desfechos positivos. Esta relação negativa pode acontecer principalmente com grupos religiosos mais rígidos e autoritários em seus dogmas e doutrinas. Tais características podem levar a uma pior saúde mental, aumentando sintomas ansiosos ou

depressivos, assim como dificultando o acesso ao tratamento médico adequado (KOENIG et al., 2001).

Embora a existência de ligações entre religiosidade e saúde mental pareça estar estabelecida, pouco se sabe sobre como os aspectos do envolvimento religioso traduz-se em resultados em saúde. Muitos mecanismos têm sido propostos, para explicar essa relação. Autores defendem que indivíduos religiosos teriam menos comportamento de risco, mais suporte social, mais enfrentamento positivo, maior senso de significado da vida, mais esperança, afeto positivo, compaixão e autocontrole (PARK, 2007).

Independente do conhecimento exato do porquê da associação positiva entre R/E e saúde mental, o estudo dessa relação continua ganhando espaço na neurociência, e se consolidando como linha de pesquisa. Desse interesse científico surgiu a necessidade de definições mais sistematizadas dos termos religião, R/E. Porém, ainda não há um consenso definido sobre eles, e, muitas vezes, ocorre sobreposição dos significados. Neste sentido, religião pode ser entendida como um sistema organizado de crenças, práticas, rituais e símbolos que são utilizados para facilitar a aproximação com o sagrado, o transcendente ou Deus. A religiosidade abrange as crenças pessoais, mescladas com crenças e práticas institucionais (KOENING et al., 2001). A espiritualidade, por sua vez, é uma busca pessoal para o entendimento de questões existenciais e suas relações com o sagrado e o transcendente, a qual pode ser vivenciada através de rituais religiosos ou não (KOENING et al., 2001).

Dessa forma, o objetivo deste artigo é fazer uma revisão clássica da literatura sobre as pesquisas publicadas nos últimos cinco anos e que envolveram a relação entre R/E com: transtorno bipolar (TB), depressão e CS.

Métodos

Trata-se de uma revisão clássica da literatura, utilizando como estratégia de busca pesquisa bibliográfica nas bases de dados *Medline*, *Scielo* e *Lilacs*. Para a seleção dos estudos, foi adotado como critério de inclusão artigos sobre R/E com desfechos clínicos referentes a: TB, depressão e CS, publicados em inglês ou português, no período de 2010 a 2015. As palavras-chave pesquisadas foram: *religiosity*, *spirituality* e seus cruzamentos com *bipolar disorder*, *affective disorders*, *depression*, *suicide*, *suicide attempt*, *suicidality*, and *suicidal behavior*. As referências bibliográficas dos artigos encontrados também foram consultadas, com o objetivo de localizar os artigos que não haviam sido detectados na busca eletrônica.

Resultados

Inicialmente, foram encontrados 525 artigos relacionados a R/E, assim distribuídos: 14 sobre TB, 344 sobre depressão; 167 sobre CS. Após a eliminação da sobreposição de resultados relacionados as diversas buscas, foram excluídos os artigos cujas populações envolviam comorbidade com doenças clínicas ou artigos, nos quais o objetivo principal fosse o estudo de outras patologias psiquiátricas, tais como esquizofrenia e transtornos de ansiedade. Assim, permaneceram 27 artigos: 5 referentes a TB, 8 sobre depressão e 14 sobre CS (ver quadros 1 e 2).

Quadro 1. Religiosidade e Transtornos de humor

AUTORES	AMOSTRA	MENSURAÇÃO RELIGIOSIDADE	RESULTADOS
Cruz et al, 2010	334 bipolares em vários estados de humor	DUKE (DRI)	Maior RNO em estados mistos e menor em eutimia
Dervic et al., 2011	149 bipolares em depressão	Filiação religiosa	Menor CS em filiados a alguma religião
Azarin et al., 2013	493 deprimidos unipolares e bipolares	DUKE (DRI)	Maior R/E, mais CS
Stroppa & Moreira 2013	168 bipolares em vários estados de humor	DUKE e <i>Brief RCOPE</i>	Maior RI, menos DP, maior QV
Caribé et al., 2015	164 bipolares tipo I eutímicos	DUKE (DRI)	Maior RI e RNO, menor CS
Gupta et al., 2011	30 deprimidos e 30 controles sadios	Escala não padronizada	Maior R/E, mais esperança, menos DP, menos CS
Pokorski & Warzecha, 2011	34 idosos com e sem depressão	<i>Religious Commitment Scale (RCs)</i>	Maior R/E sem associação com DP
Lupo & Strous, 2011	119 estudantes de medicina com e sem depressão	Escala não padronizada	Maior R/E, maior ansiedade, sem associação com DP
Miller et al., 2012	114 indivíduos com risco de desenvolver depressão	Escala não padronizada	Maior R/E, menor DP
Balbuena et al., 2013	12.583 deprimidos	Escala não padronizada	Maior RO, menor DP
Bennett & Shepherd, 2013	278 mulheres com depressão	<i>Daily Spiritual Experience Scale (DSES)</i>	Maior R/E, maior SS, menor DP
Ronneberg et al., 2014	1992 deprimidos e 5740 não deprimidos	<i>The Leave Behind Questionnaire</i>	Maior RO e RNO, menor DP
Mosqueiro et al., 2015	143 deprimidos internados	DUKE (DRI)	Maior RI, maior resiliência, menor DP

CS=comportamento suicida, R/E= religiosidade/espiritualidade, QV= qualidade de vida, SS= suporte social, DP = depressão, RI=religiosidade intrínseca, RNO=religiosidade não organizacional, RO=religiosidade organizacional

Quadro 2. Religiosidade e Comportamento Suicida

AUTORES	AMOSTRA	MENSURAÇÃO DA RELIGIOSIDADE	RESULTADOS
Zhang et al, 2010	392 suicidas e 416 controles	Filiação, crença em Deus, crença vida após a morte	Maior R/E, maior CS
Rasic et al., 2011	1615 adolescentes saudáveis	Escala não padronizada	Maior R/E, menor DP e uso drogas
Taylor et al., 2011	6.082 imigrantes	Escala não padronizada	Maior R/E, Menor CS
Robinson et al., 2012	20.130 adultos	Escala não padronizada	Maior R/E, Menor CS
Nkansah-Amankra et al., 2012	9412 adultos	Frequência encontro religioso + RNO	R/E associado a maior SS
Caribé et al., 2012	110 pacientes com TS e 114 controles	DUKE (DRI)	Maior RI, RO, RNO, menor CS
Rushing et al., 2013	248 idosos deprimidos	Religiosidade privada	Maior R/E, maior SS, menor CS
Amit et al., 2014	620 adolescentes judeus	Escala não padronizada	Maior R/E, menor CS
Hoffman & Marsiglia, 2014	700 estudantes	Religiosidade intrínseca e extrínseca	Maior R/E, menor CS
Rieger et al., 2014	1200 estudantes universitários	<i>Religious Faith Questionnaire</i> (SCSORF)	Maior R/E, Maior sentido na vida, menor CS
Wilchek-Aviad & Malka, 2014	450 estudantes judeus	<i>The Purpose in Life Questionnaire</i> (PIL)	Maior R/E, maior sentido na vida, menor CS
O'Reilly & Rosato, 2015	1.106.104 adultos	Filiação	Sem associação entre filiação e CS
Toussaint et al, 2015	4448 adultos jovens	Filiação + escala não padonizada	Maior R/E, menor CS
Caribé et al., 2015	93 pacientes com doença mental e 61 controles saudáveis	DUKE (DRI)	Maior R/E, menor Impulsividade, menor CS

CS=comportamento suicida, R/E= religiosidade/espiritualidade, QV= qualidade de vida, SS= suporte social DP = depressão, RI=religiosidade intrínseca, RNO=religiosidade não organizacional, RO=religiosidade organizacional, ER = enfrentamento religioso

Discussão

Religiosidade/Espiritualidade e Transtorno Bipolar

O TB é uma doença psiquiátrica que traz impactos negativos na qualidade de vida (QV) e no funcionamento social e cognitivo dos seus portadores (GEDDES & MIKLOWITZ, 2013). Recentes estudos demonstram que a religiosidade pode atuar como ferramenta de enfrentamento e resiliência frente a doença mental, porém há uma carência de estudos sistemáticos sobre a relação entre R/E e TB (De FAZIO et al., 2015).

Em 2010, Cruz e colaboradores estudaram, pela primeira vez, a associação entre as diversas fases do TB com as três principais dimensões da religiosidade mensuradas pela escala de religiosidade de Duke (DRI), que é dividida em: religiosidade organizacional (RO), religiosidade não organizacional (RNO) e religiosidade intrínseca (RI). Neste estudo, com 334 pacientes ambulatoriais, verificou-se que as taxas de oração e meditação foram maiores entre aqueles que estavam em estado misto e menor entre aqueles que estavam em eutímia. Pacientes em fase depressiva ou maníaca não apresentaram associação significativa com nenhuma das dimensões da religiosidade. Esses autores sugeriram que a maior gravidade e o pior prognóstico dos estados mistos podem ser razões para um aumento na frequência do comportamento de religiosidade privada como uma estratégia de enfrentamento (CRUZ et al., 2010). No entanto, a maneira como as dimensões da R/E podem mudar de acordo com as alterações do humor ainda não são bem compreendidas (AUBIN, 2010).

Um estudo que avaliou pacientes com TB, em fase depressiva, encontrou menos história de CS naqueles com filiação religiosa comparado aos pacientes sem filiação. Neste estudo, um provável mediador entre menor CS e filiação religiosa, pode ter sido a objeção moral ao CS, promovida pela religião (DERVIC et al., 2011). Outro trabalho que avaliou 168 pacientes bipolares ambulatoriais encontrou uma forte associação entre maior RI e enfrentamento religioso positivo com menos sintomas depressivos e melhor QV (STROPPIA & MOREIRA ALMEIDA, 2013).

Em recente estudo, Caribé e colaboradores (2015) avaliaram pacientes com TB, sob rígidos critérios de eutímia, na tentativa de se eliminar as possíveis distorções frequentes nas fases agudas da doença, e mostraram uma relação inversa entre

maiores níveis de RI e RNO, com história de CS, mesmo após controle de importantes variáveis clínicas e sócio-demográficas que poderiam interferir no desfecho em questão (CARIBÉ et al., 2015).

Entretanto, em contraste com os resultados de que a religiosidade protege o paciente com TB em relação ao CS, um estudo que comparou pacientes deprimidos com baixo envolvimento religioso (LRI) com aqueles com alto envolvimento religioso (HRI), concluiu que HRI associado a características mistas pode aumentar o risco de CS, apesar da existência de filiação religiosa (AZORIN et al., 2013). Os autores também sugerem que, nestes casos, é provável que o envolvimento religioso possa agravar sentimentos de culpa ou o caráter pecaminoso de suas experiências hipomaniacas, reforçando assim as tendências suicidas. No entanto, é importante salientar que, neste estudo, os autores incluíram uma amostra heterogênea, com pacientes com depressão unipolar e com depressões pertencentes ao espectro bipolar que tiveram hipomania espontânea ou associada ao uso de antidepressivos (AD). Além disso, a medida de religiosidade pode ter gerado viés no ponto de corte para LRI e HRI, pois a DRI foi avaliada na sua pontuação total, sem levar em consideração suas três dimensões separadamente, o que não é recomendado pelos autores da própria escala (KOENIG et al., 1997; LUCCHETTI et al., 2012).

Apesar dos resultados descritos, as relações entre R/E no TB ainda carecem de maiores investigações, porém os poucos dados disponíveis apontam para um efeito protetor da R/E em relação a: menor CS, menos sintomas depressivos e melhor QV.

Religiosidade/Espiritualidade e Depressão

Uma revisão sistemática que envolveu um total de 98.975 indivíduos, mostrou uma relação inversa entre sintomas depressivos e envolvimento religioso (SMITH, 2003). Interessante salientar que, estudos publicados nos últimos cinco anos corroboram os resultados desta revisão sistemática, como a pesquisa de Miller et al., 2012 que acompanhou por 10 anos, 114 adultos sob risco de desenvolver quadros depressivos. Nesta pesquisa, os indivíduos que consideraram a R/E importante para suas vidas tiveram menor risco de desenvolver depressão ao longo do seguimento. Porém, frequência a encontros religiosos e a filiação religiosa não demonstraram

resultados significativos. Ao contrário dos resultados do estudo realizado no Canadá, com 14 anos de seguimento que identificou que a frequência de pelo menos ir uma vez ao mês a encontros religiosos tem um efeito protetor em relação ao desenvolvimento de depressão (BALBUENA et al., 2013).

Outro estudo longitudinal acompanhou por 2 anos, 1992 pacientes com depressão e 5740 sem depressão. No início do estudo, no grupo dos não deprimidos, a maior frequência a encontros religiosos exerceu um efeito de proteção em relação a possibilidade de desenvolver depressão ao longo do acompanhamento. Da mesma maneira, os pacientes com depressão foram menos propensos a ter recorrência da doença no seguimento, se tivessem mais envolvimento na prática da religiosidade privada. Os resultados sugerem que ambas as formas de religiosidade (RO e RNO) podem afetar o curso da depressão, seja no desencadeamento ou na recorrência dos sintomas, respectivamente (RONNEBERG et al., 2014).

Em estudo de corte transversal que comparou pacientes deprimidos com alto e baixo nível de religiosidade, constatou-se que aqueles com alta R/E apresentaram mais esperança e menos CS (GUPTA et al., 2011).

Vale ressaltar que, além de demonstrar efeito protetor na população geral e em pacientes psiquiátricos, pesquisas apontam que o efeito positivo da R/E também ocorre em portadores de outras doenças clínicas, tais como neoplasias, nos quais a R/E proporciona não apenas a melhora da QV, assim como esta inversamente relacionada a depressão (KANDASAMY et al., 2015; JANG et al., 2013; LYNCH et al., 2012; JOHNSON et al., 2011). Esses resultados têm uma relevância clínica, pois a presença, a gravidade e a duração de quadros depressivos influenciam negativamente no prognóstico de algumas patologias (ALDEA et al., 2014; LICHTMAN et al., 2014).

Recentemente, apenas dois trabalhos trazem resultados que vão de encontro a maioria dos achados da literatura que mostram benefício da religiosidade no desfecho dos transtornos de humor. Um deles, um corte transversal que avaliou, 34 idosos poloneses e não encontrou associações significativas entre maior religiosidade e menor depressão nesta população. Porém, devido ao número muito limitado de participantes, a análise pode ter sido prejudicada (POKORSKI & WARZECHA, 2011). Outra pesquisa de corte transversal realizada com 119 estudantes universitários do curso de medicina em Tel Aviv, não encontrou relação significativa entre religiosidade

e depressão, mostrando uma relação positiva entre maior religiosidade e ansiedade (LUPO & STROUS, 2011). Os autores acreditam que um enfrentamento religioso negativo, permeado por rigidez e autocobrança excessiva podem justificar esta relação positiva entre R/E e ansiedade.

Em linhas gerais, da mesma forma que no TB, ainda não se conhecem os mecanismos exatos que medeiam as relações entre religiosidade e depressão. Porém, pesquisadores sinalizam que fatores como maior suporte social e maior resiliência decorrentes de uma maior R/E, possam explicar parcialmente os efeitos positivos da R/E nos quadros depressivos (MOSQUEIRO et al., 2015; KASEN et al., 2012; BENNETT & SHEPHERD, 2013).

Religiosidade/ Espiritualidade e Comportamento Suicida

A maior parte da pesquisa médica e social sobre os fatores associados ao suicídio tem se concentrado nos chamados fatores de risco, sendo assim, atualmente, as evidências sobre o papel dos fatores de proteção contra o CS são escassas. Diante disso, a R/E vem se destacando como importante fator de proteção ao CS (COLUCCI & MARTIN, 2008).

O primeiro método desenvolvido para abordar esse tema foi à investigação das relações entre a afiliação a um grupo religioso e as taxas de suicídio. O trabalho clássico de Durkheim intitulado “O suicídio” (1897), foi o ponto de partida para a pesquisa acerca das relações entre religião e suicídio. Ele comparou as taxas de suicídio de diversos países, levando em conta a religião predominante em cada um deles. Seus achados basicamente apontaram para uma incidência de suicídios 50% maior nos países protestantes em relação aos de maioria católica (DURKHEIM, 2004).

Importante salientar que, a teoria sociológica e os estudos ecológicos iniciados por Durkheim têm produzido resultados controversos. Duas das principais críticas foram a ausência de controle de variáveis de confusão e o risco de se fazer inferências causais em relação a indivíduos, tendo como base observações de agregados populacionais. Além disso, investigar apenas a filiação religiosa não traduz a completa vivência espiritual do indivíduo.

Nesta mesma linha de pesquisa, um recente trabalho que seguiu por nove anos, mais de um milhão de pessoas, com o objetivo de avaliar a relação entre filiação religiosa e risco de suicídio mostrou que não houve diferença significativa em relação ao risco de suicídio quando comparados indivíduos com ou sem filiação religiosa. Exceto em relação a pequena amostra de indivíduos filiados a religiões conservadoras, nos quais houve um efeito de proteção em relação ao suicídio quando comparados aos não filiados ou filiados a religiões não ortodoxas (O'REILLY & ROSATO, 2015). Estes achados corroboram a ideia de que muito mais importante do que a filiação, é o nível de envolvimento espiritual e religioso dos indivíduos (ROBINSON et al., 2012; TAYLOR et al., 2011).

Em relação a adolescentes, a religiosidade parece também exercer um efeito protetor ao CS, como demonstrado em pesquisa que acompanhou mais de nove mil jovens e identificou que a participação em atividades religiosas está associada com menor taxa de suicídio. Porém, outros fatores como suporte familiar e social podem ter influenciado nesses resultados (NKANSAH-AMANKRA et al., 2012). De fato, pesquisas com adolescentes em diferentes populações têm demonstrado resultados semelhantes em Israel, Trinidad Tobago e México (AMIT et al., 2014; TOUSSAINT et al., 2015, HOFFMAN & MARSIGLIA, 2014). Esses autores mostraram que maiores níveis de religiosidade estavam significativamente relacionados a menor automutilação, menos pensamento ou CS, mesmo após controle de outros fatores importantes nesse desfecho (TOUSSAINT et al., 2015; AMIT et al., 2014; HOFFMAN & MARSIGLIA, 2014).

No Brasil, um estudo de caso controle que comparou 110 indivíduos que tentaram suicídio por uso de substâncias, com 114 indivíduos sem história de TS, mostrou que mesmo após o controle de variáveis sociodemográficas, presença ou ausência de doença mental e níveis de impulsividade, o nível de RO, RNO e RI foram inversamente associadas a TS (CARIBÉ et al., 2012).

De modo geral, a vivência religiosa parece exercer um efeito protetor em relação ao amplo espectro do CS, desde ideação, tentativas e suicídio consumado. Porém, algumas pesquisas feitas em populações com alguma especificidade cultural ou psicopatológica, obtiveram resultados contrários, a exemplo de um estudo de caso controle realizado em população rural, na China, no qual a R/E foi associada a um maior risco de CS (ZHANG et al., 2010). Questões específicas da vivência religiosa desta população podem justificar

estes achados. Assim como, o estudo já mencionado de Azorin e colaboradores (2013), que encontrou relação positiva entre maiores níveis de religiosidade e CS em indivíduos deprimidos pertencentes ao espectro bipolar, e o estudo de Trevino (2014) que identificou associação positiva entre enfrentamento religioso negativo e maior ideação suicida em pacientes com câncer (TREVINO et al., 2014).

Apesar da forte associação inversa entre R/E e CS, ainda não se sabe exatamente quais mecanismos podem mediar esta relação. Há algumas hipóteses que ainda necessitam de confirmação, tais como um maior suporte social promovido pelas religiões (RUSHING et al., 2013), menor uso de álcool e drogas (RASIC et al., 2011), menor impulsividade (CARIBÉ et al., 2015), menos depressão, maior resiliência (MOSQUEIRO et al., 2015), mais sentido da vida e mais esperança (RIEGER et al., 2014; WILCHEK-AVIAD & MALKA, 2014).

Conclusões

Os resultados da maioria das pesquisas sobre as relações entre R/E e transtornos de humor demonstram que maiores níveis de R/E se associam a uma diminuição da intensidade, da recorrência e da duração dos episódios depressivos, com melhor QV, mais enfrentamento da doença e menos CS. Porém, pesquisas futuras devem se dedicar a melhor compreensão do porquê uma maior religiosidade se traduz em melhores desfechos em saúde, buscando identificar quais são os fatores de mediação, para futuramente se avaliar possíveis aplicações deste conhecimento na prática clínica.

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4 ARTIGOS ORIGINAIS

4.1 ARTIGO Nº 1: RELIGIOSITY AND IMPULSIVITY IN MENTAL HEALTH IS THERE A RELATIONSHIP?

Religiosity and Impulsivity in Mental Health Is There a Relationship?

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Religiosity and Impulsivity in Mental Health *Is There a Relationship?*

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Abstract: Our aim is to evaluate the relationship between religiosity and impulsivity in patients with mental illness who had attempted suicide and in healthy individuals. This is a cross-sectional study that included 61 healthy individuals and 93 patients. The instruments used were a sociodemographic data questionnaire, the Mini International Neuropsychiatric Interview, the Barratt Impulsiveness Scale, and the Duke University Religion Index. The healthy individuals presented higher scores in the religiosity domains (organizational, $p = 0.028$; non-organizational, $p = 0.000$; intrinsic, $p = 0.000$). The patients presented higher scores in the impulsivity dimensions (attentional, $p = 0.000$; motor, $p = 0.000$; absence of planning, $p = 0.000$). In the patient group, intrinsic religiosity had a significant inverse relationship with total impulsivity ($p = 0.023$), attentional ($p = 0.010$), and absence of planning ($p = 0.007$), even after controlling for sociodemographic variables. Healthy individuals were more religious and less impulsive than patients. The relationship between religiosity, impulsiveness, and mental illness could be bidirectional; that is, just as mental illness might impair religious involvement, religiosity could diminish the expression of mental illness and impulsive behaviors.

Key Words: Religiosity, impulsivity, mental health

(*J Nerv Ment Dis* 2015;203: 551–554)

In recent decades, researchers have become more interested in scientifically studying the relationships between religiosity and health outcomes (Moreira-Almeida et al., 2006). Despite some methodological controversy, most of the studies that have been conducted to date show that greater religious involvement is positively associated with indicators of psychological well-being and better health (Dein et al., 2012; Koenig et al., 2001). In fact, the level of religious involvement tends to be inversely related to depression, suicidal behavior, and drug misuse (Bonelli and Koenig, 2013; Ronneberg et al., 2014). Although a number of articles have shown a protective effect of religious involvement against mental illnesses, rarely have the potential mediators of this relationship been investigated (Moreira-Almeida et al., 2006). In this context, one possible mediator could be impulsivity.

Impulsivity is a complex phenotype characterized by a variety of cognitive and behavioral patterns that lead to immediate, medium-, and long-term dysfunctional consequences (von Diemen et al., 2007). Over the last few decades, many studies on impulsivity have highlighted the importance of this symptom in various mental disorders, such as

personality disorders, bipolar disorder, suicidal behavior, pathological gambling, and drug misuse (Ledgerwood and Petry, 2004; Saddichha and Schuetz, 2014; von Diemen et al., 2007). In this context, although some studies indicate that there is an inverse relationship between religious practices and impulsivity, this topic has not been completely investigated (Patoock-Peckham et al., 1998; Pearson et al., 1986). Thus, our aim is to evaluate the relationship between religiosity and impulsivity in patients with mental illness who have attempted suicide and in healthy individuals.

SUBJECTS AND METHODS

The patients involved in this study were part of a continuous assessment project that studied individuals who had attempted suicide by means of substances and who had been admitted to an anti-poison information center (CIAVE, Salvador, Brazil) (Caribé et al., 2012). CIAVE is a public service emergency center located within a general hospital (Hospital Geral Roberto Santos) that admits patients who have attempted suicide by substance use. A suicide attempt (SA) was defined as the use of toxic substances, such as medications, or chemical products with the intention of causing one's own death. All patients were 18 years or older and had been admitted to the emergency room at CIAVE for SA between July 2009 and July 2010. The patients were interviewed at CIAVE within 15 days of clinical rehabilitation for SA and, on average, within 5 days after they had attempted suicide. This study only assessed individuals with mental health issues that had been diagnosed according to the Mini International Neuropsychiatric Interview (M.I.N.I.PLUS).

The control group consisted of the people who had accompanied these patients, their relatives, and unrelated individuals who were from the same community to prevent any bias associated with differences in sociodemographic data between the groups. The selection criteria were controls of the same age and gender as the patients under assessment who had neither a history of previous SA nor an Axis I mental disorder. The data were collected using the same instruments for both patients and controls.

The instruments used were (1) a clinical and sociodemographic questionnaire, (2) the M.I.N.I.PLUS for the diagnosis of Axis I psychiatric disorders (Amorim, 2000), and (3) the Duke University Religion Index (DUREL). The DUREL is a five-item self-report scale that assesses three domains of religiosity: organizational religiosity (OR), non-organizational religiosity (NOR), and intrinsic religiosity (IR). The OR domain is measured with one item and is defined as the frequency with which one attends formal religious services. The NOR domain is measured with one item and is defined as the amount of time spent in private religious activities, such as prayer or meditation. The IR domain is measured with three items and is conceptualized as the degree to which one has integrated religion into one's life (Lucchetti et al., 2012). The religiosity evaluation assessed the period beginning 1 year before the SA, and (4) The Barratt Impulsiveness Scale (BIS 11) assessed Attentional Impulsiveness (AI), Motor Impulsiveness (MI), Absence of Planning (AP), and Total Impulsivity (TI) (von Diemen et al., 2007). All instruments were validated in Brazilian Portuguese.

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TABLE 1. Sociodemographic and Clinical Characteristics of Participants

Variables	Patients (n = 93) N (%) Mean ± SD	Healthy (n = 61) N (%) Mean ± SD	p-Value
Age (yr)	34.4 (10.3)	33.6 (11.1)	0.165
Gender (% female)	50 (53.7%)	35 (57.4%)	0.659
Employment (% employed)	56 (60.2%)	40 (65.5%)	0.502
Has partner	46 (49.5%)	34 (55.7%)	0.446
Has children	34 (36.62%)	32 (52.5%)	0.051
Has religious affiliation	51 (54.8%)	35 (57.4%)	0.756
Impulsiveness			
Attentional	21.1 (4.35)	17.8 (3.93)	0.000
Motor	23.4 (6.87)	17.5 (5.14)	0.000
Planning	27.7 (5.93)	21.5 (4.45)	0.000
Total	72.3 (15.41)	56.2 (11.69)	0.000
Religiosity			
Organizational	3.01 (1.53)	3.59 (1.54)	0.028
Non-organizational	2.92 (1.63)	4.44 (1.55)	0.000
Intrinsic	7.27 (3.42)	12.6 (2.55)	0.000

This study was approved by the local Medical Review Ethics Committee and performed according to the ethical standards set in the 1964 Declaration of Helsinki. Additionally, all patients provided written informed consent before their inclusion in the study.

Statistical Analysis

Descriptive analysis was conducted on the scores in the religiosity (OR, NOR, IR) and impulsiveness domains (AI, MI, AP, TI) between the patients and the healthy controls. Simple frequencies and percentages of the categorical variables were obtained, as were measures of the central tendencies (mean values) and dispersions (standard deviations) of the numerical variables. To verify the possible differences in clinical and sociodemographic characteristics between the two groups, the chi-square test and Student's *t*-test were used. After this initial analysis, the variables that showed a potentially statistically significant difference ($p \leq 0.20$) between the groups were adjusted in the multivariate regression.

The goodness-of-fit model adjustment was verified by the R-squared and adjusted R-squared, and the significance level adopted for the regression analysis was 5% ($p \leq 0.05$). The coefficient (β) and confidence intervals of 95% (95% CI) were obtained by multivariate analysis using the linear regression model, adjusted for the probable confounding variables of age and having children ($p \leq 0.20$). This methodology enabled estimating the mean increases (or decreases) in the outcomes of a number of variables. The collected data were digitized using the Statistical Package for Social Sciences software (SPSS Win, version 16) and were analyzed in the statistical program Stata v. 12.0.

RESULTS

One hundred thirty-nine patients with SA were eligible to participate in the study during the period between July 2009 and July 2010. Twelve (8.6%) refused to participate, 17 (12.2%) left the hospital too soon to be evaluated, and 17 were excluded because they did not meet the criteria for a mental disorder, resulting in a total of 93 patients. In addition, during the course of the study, 11 patients died from suicide before they had been selected for the study. Among the healthy individuals, 124 were eligible to participate, 10 (8.0%) were excluded because of previous SA, and 53 (42.7%) were excluded because they had a mental disorder, giving a total of 61 healthy controls.

The healthy individuals presented higher scores in the religiosity domains compared with the patients: OR ($p = 0.028$); NOR ($p = 0.000$),

and IR ($p = 0.000$). The patients presented higher scores in the impulsivity domains compared with the healthy individuals' AI ($p = 0.000$), MI ($p = 0.000$), AP ($p = 0.000$), and TI ($p = 0.000$). The clinical and sociodemographic data are described in Table 1.

Among the patients, 57 (61.2%) had major depression (MD), 20 (21.5%) had generalized anxiety disorder (GAD), 18 (19.3%) had alcohol dependence, 9 (9.6%) had bipolar disorder, 8 (8.6%) had drug dependence, 7 (7.5%) had schizophrenia, 8 (8.6%) had panic disorder, and 24 (25.8%) had other illnesses. Of the patients with MD, 30 (52.6%) presented with psychiatric comorbidities, as did 17 (85%) of those with GAD.

In the patient group, IR showed an inverse relationship with all impulsivity domains, with TI ($p = 0.023$), AI ($p = 0.010$), and AP ($p = 0.007$) being significant even after controlling for probable confounding variables. In this group, NOR and OR did not demonstrate a significant relationship. Among the healthy individuals, there were no statistically significant relationships between the religiosity and impulsivity domains (Table 2). Regarding the components OR, NOR, and IR, the coefficient of the explanation for the linear regression models adjusted for the healthy individuals and the patients varied from 0.18 to 0.30 and from 0.07 to 0.20, respectively.

DISCUSSION

The literature shows the presence of mental illness as one of the main risk factors for suicidality (Henriksson et al., 1993; Suominen et al., 1996). However, mental illness per se is unable to explain the entire complexity of suicidality. In this study, mentally ill patients who had attempted suicide were evaluated, as were healthy controls, by measuring levels of impulsivity and religiosity to analyze the relationship between the two.

In this context, bivariate analysis showed that the patients had much higher impulsivity levels and lower levels of religiosity in all domains than did the healthy controls, suggesting that the behavioral profile of greater religiosity and lower impulsivity may be a protective factor against SA (Caribé et al., 2012; Sisask et al., 2010).

The hypothesis that greater levels of religiosity are associated with less impulsivity has been strengthened by studies using positron emission tomography that revealed that religious practice stimulates the limbic system, increasing the activity of the autonomic centers of the nervous system, such as the hypothalamus, amygdala, and hippocampus (Newberg et al., 2001), modifying brain function, and reducing

TABLE 2. Religiosity and Impulsivity Domains in Healthy Controls and Patients

	Total Impulsivity		Attentional		Motor		Non-Planning	
	<i>B</i>	95% CI	β	95% CI	β	95% CI	β	95% CI
Controls								
OR	-1.21	[-3.03; 0.61]	-0.35	[-0.97; 0.25]	-0.49	[-1.34; 0.36]	-0.35	[-1.09; 0.37]
NOR	-1.07	[-2.80; 0.64]	-0.27	[-0.84; 0.30]	-0.32	[-1.13; 0.48]	-0.48	[-1.17; 0.20]
IR	-0.78	[-1.90; 0.33]	-0.21	[-0.59; 0.15]	-0.41	[-0.93; 0.10]	-0.14	[-0.60; 0.30]
Patients								
OR	-1.01	[-3.25; 1.23]	-0.35	[-0.96; 0.26]	-0.42	[-1.44; 0.58]	-0.23	[-1.10; 0.63]
NOR	0.42	[-1.56; 2.42]	-0.07	[-0.62; 0.47]	0.48	[-0.41; 1.37]	0.02	[-0.75; 0.79]
IR	-1.05	[-1.95; -0.14]*	-0.32	[-0.56; -0.07]*	-0.25	[-0.67; 0.16]	-0.47	[-0.82; -0.12]*

OR indicates organizational religiosity; NOR, non-organizational religiosity; IR, intrinsic religiosity; CI, confidence intervals.
* $p < 0.05$.

cortisol and pro-inflammatory interleukin plasmatic levels (Carrico et al., 2006; Lutgendorf et al., 2004). Additionally, religious practice promotes increased prefrontal cortex metabolism (Newberg et al., 2001) that in turn influences impulse control, decision-making, and moral judgments (Seybold, 2007). Moreover, other studies show an inverse relationship between religiosity, pathological gambling, and drug use, conditions generally associated with high levels of impulsivity (Ghandour and El Sayed, 2013; Gomes et al., 2013).

Therefore, greater religiosity is potentially related to less impulsivity. However, this could be altered by other factors, such as mental illness, as was found in the current study (Crews and Boettiger 2009; Estevez et al., 2013; Odlaug et al., 2013). We presume that healthy individuals can more easily practice their religiosity in its principal aspects, such as going to church (OR), meditating or praying (NOR), and incorporating religiosity into their lives (IR), without the cognitive and psychosocial impairments caused by mental illness (Iosifescu, 2012).

In the patient group, the inverse relationship between IR and the impulsivity domains, especially TI, AI, and AP, even after controlling for age and having children, may indicate that IR reflects the internalization of religious commitment in an individual's life. IR may become more stable and likely less influenced by the presence of mental illness. Incorporation of religiosity, among the religious dimensions, is most likely to correlate with the neural substrate that underlies religiosity because it can become a way of life that is lived, experienced, and continuously sustained (Hill et al., 2000; Muramoto, 2004). Thus, it would be less compromised by the presence of mental illness. Nevertheless, in this study, regarding the healthy individuals, the relationship between IR and the impulsivity domains, although it was inverted, was not significant, most likely because of the small number of controls evaluated.

Indeed, cross-sectional studies show that religiosity is associated with greater self-control and with personality traits such as amiability, conscientiousness, and empathy (McCullough and Willoughby, 2009; Pearson et al., 1986). Other longitudinal studies show that religious families tend to have less impulsive children who have more self-control (Bartkowski et al., 2008). Hence, greater religiosity during adolescence may positively mold personality traits in adulthood (Wink et al., 2007). However, other studies suggest that specific personality traits determine whether the individual becomes more or less religious (McCullough and Willoughby, 2009; Wink et al., 2007). Regardless, these results suggest that religious experience may reduce the expression of impulsivity, which could in and of itself decrease suicidality.

It is important to note that this complex relationship between religiosity, impulsiveness, mental illness, and suicidal behavior could be bidirectional; that is, just as mental illness might impair religious involvement, religiosity could, through multiple mechanisms, diminish

the expression of mental illness and impulsive behaviors and dissuade one from suicide (Seybold, 2007; Park, 2007).

Certain limitations are inherent in this work. This was a cross-sectional study; therefore, cause and effect relationships were not evaluated. The sample size was small, and all of the patients had been part of a subgroup of people who had attempted suicide by means of substances, warranting caution in interpreting the results. Additionally, because of the study's size, the patients were not evaluated for specific pathologies, which should be conducted in future studies.

Our data reveal that healthy individuals are more religious and less impulsive than are patients with mental disorders, suggesting that the presence of a mental illness may modify the relationship between impulsivity and religiosity or religiosity may affect the relationship between impulsivity and mental illness. Future research could help us to answer these questions.

DISCLOSURES

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The authors declare no conflict of interest.

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4.2 ARTIGO Nº 2: IS RELIGIOSITY A PROTECTIVE FACTOR AGAINST
SUICIDAL BEHAVIOR IN BIPOLAR I OUTPATIENTS?

**Is religiosity a protective factor against
suicidal behavior in bipolar I outpatients?**

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Is religiosity a protective factor against suicidal behavior in bipolar I outpatients?



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ABSTRACT

Background: Several risk factors have been associated with suicidal behavior (SB) in bipolar disorder (BD), but little is known regarding possible protective factors. Religiosity has been related to favorable outcomes in mental health and to a reduction in the risk of SB, although the relation between BD, religiosity and SB remains under-investigated. The objective of this study was to evaluate the association between religiosity and SB in euthymic bipolar I outpatients.

Method: In this study, 164 outpatients with BD type I with and without a history of suicide attempts were assessed and compared using a questionnaire to collect clinical and sociodemographic characteristics, the Structured Clinical Interview for DSM-IV, the Hamilton Depression Rating Scale, the Young Mania Rating Scale, the Duke Religious Index, and the Barratt Impulsivity Scale.

Results: The suicide attempters (SA) group had more psychiatric comorbidity ($p=0.007$), more rapid cycling ($p=0.004$), higher levels of impulsivity in all domains ($p=0.000$), and less religious affiliation ($p=0.006$) compared with the non-SA group. In the multivariate analysis, after controlling for covariates, non-organizational religious activities (OR, 0.66; 95% CI, 0.50–0.86) and intrinsic religiosity (OR, 0.70; 95% CI, 0.60–0.81) were associated with less SB.

Limitations: A small sample size, the cross-sectional design that precluded the possibility of assessing cause and effect relationships, and the infeasibility of determining the time lapse between the last suicide attempt and the period when the patients were evaluated.

Conclusion: Non-organizational religious activities and intrinsic religiosity dimensions exert a protective effect against SB in bipolar I outpatients, even when controlling for variables that may affect the outcome in question.

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1. Introduction

Suicide is a major public health issue that results in approximately one million deaths per year worldwide (Pompili et al., 2013; Wasserman et al., 2012). It is estimated that there are 10–40 attempted suicides for each completed suicide (Bertolote et al., 2006). Despite the complexity of this issue and the need for the interaction of multiple factors for suicidal behavior (SB) to

manifest, the presence of mental illness is one of the most important factors in the occurrence of this outcome (Randall et al., 2014).

Among mental illnesses, bipolar disorder (BD) is one of the illnesses that is most frequently associated with suicide attempts and suicide (Chesney et al., 2014). In the Epidemiological Catchment Area study (ECA), 29% of individuals with BD in the general population made at least one suicide attempt during their lifetime (Chen and Dilsaver, 1996). In clinical samples, 25–56% of patients with BD report at least one suicide attempt during their lives, and 10–19% die by suicide (Costa et al., 2015; Parmentier et al., 2012). For the most part, the focus of research on SB aims to understand the risk factors; however, little attention has been devoted to

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investigating the protective factors against SB in bipolar patients (Latalova et al., 2014).

In recent decades, researchers have become more interested in scientifically studying the relationships between religiosity and mental health (Caribé et al., 2015; Moreira-Almeida et al., 2006). Most of the studies that have been conducted to date show that greater religious involvement is positively associated with indicators of psychological well-being and better health (Dein et al., 2012; Koenig et al., 2001). In fact, level of religious involvement tends to be inversely related to depression, SB, drug misuse, impulsivity, and pathological gambling (Casey et al., 2011; Ronneberg et al., 2014; Caribé et al., 2012). With regard to SB, the studies entailed heterogeneous samples of patients presenting with several mental illnesses (Wu et al., 2015). However, what little research there is on patients with mood disorders suggests that religiosity bestows a protective effect against SB in this population (Mosqueiro et al., 2015).

Although the existence of links between religiosity and health appear to be established, much less is known about how these aspects of religious involvement translate into health outcomes. Many mechanisms have been proposed to account for these relationships, with those most commonly mentioned including health behaviors, social support, coping, a sense of meaning in life, hope, positive affect, compassion, and locus of control (Park, 2007). However, the relationship between religiosity and BD continues to be under-investigated, and the hypothesis that religiosity can be relevant both in terms of providing a protective effect and as a provocative element in SB, depressive or manic/hypomanic phases in BD has not been fully supported (De Fazio et al., 2015). Moreover, some studies on BD have included non-homogeneous patient samples, such as BD type I and II, and have used various methodologies, making it difficult to compare the results (Bonelli and Koenig, 2013; De Fazio et al., 2015). Therefore, the objective of this study was to evaluate whether there is an association between religiosity and SB in bipolar I outpatients evaluated only in a euthymic state.

2. Methods

2.1. Participants

The sample was composed of outpatients aged 18 years or older with BD type I according to DSM-IV criteria. All were included during the 2012–2014 period at four specialized centers for the treatment of BD in Brazil: 1-Program of mood and anxiety disorders of the Federal University of Bahia-CETHA-(UFBA), Salvador-Bahia; 2-Interdisciplinary Laboratory of Clinical Neurosciences, Federal University of São Paulo-(UNIFESP)-São Paulo-São Paulo; 3-Laboratory of Molecular Psychiatry, INCT for Translational Medicine, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre- Rio Grande do Sul; 4-Department of Mental Health of the Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais.

Inclusion criteria were as follows: being in a euthymic state, defined as having scores lower than 7 on both the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) and no mood episodes in the previous two months. The exclusion criterion was difficulty in understanding the questionnaires.

After administering the protocol, the patients were divided into two groups: suicide attempters (SA) and non-suicide attempters (non-SA). The SA group was composed of patients who reported at least one suicide attempt during their lifetime. The information on history of suicide attempt(s) is collected in the questionnaire of clinical and sociodemographic data, which includes presence or

absence thereof, number of attempts and method. A suicide attempt was defined as any act of self-inflicted injury with the intention of causing one's own death.

This study was approved by the local Medical Review Ethics Committee and performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki. In addition, all patients provided written informed consent prior to their inclusion in the study.

2.2. Instruments

This was a cross-sectional study in which data were collected using the same instruments at all centers. Face-to-face interviews were conducted simultaneously with the scale application. The interviews were conducted individually or, when necessary, in the presence of family members. The data gathered from the patients' reports were complemented by the data in the medical chart, as appropriate. The evaluations were performed by psychiatrists who had been trained in using the referred instruments and had more than 5 years of experience in the field. The instruments used are described as follows:

(1) a questionnaire to collect clinical and sociodemographic characteristics; (2) a structured clinical interview with DSM-IV axis I (SCID-I) for the diagnosis of mental illnesses (First et al., 1997); (3) the Duke Religious Index-DUREL-(DRI), a five-item self-report scale that assesses three domains of religiosity: organizational religious activities (ORA), non-organizational religious activities (NORA), and intrinsic religiosity (IR). The ORA domain is measured by one item and defined as the frequency with which one attends formal religious services. The NORA domain is measured by one item and defined as the amount of time spent in private religious activities such as prayer or meditation. The IR domain is measured by three items and conceptualized as the degree to which one integrates one's religion into one's life. Response options were on a 5- or 6-point Likert scale (Lucchetti et al., 2012); and (4) the Barratt Impulsivity Scale (BIS-11), a 30-item self-report measure of impulsivity that includes three subscales: (i) attentional (AI) (problems related to concentrating and/or paying attention), (ii) motor (MI) (fast reactions and/or restlessness), and (iii) non-planning (AP) (orientation toward the present rather than the future) and total impulsivity (TI) (von Diemen et al., 2007). All instruments were validated in Brazilian Portuguese.

2.3. Statistical analysis

The collected data were recorded using the Statistical Package for Social Sciences (SPSS Win, v. 16) and were analyzed in the statistical program Stata v. 9.0. The simple frequencies and percentages of the categorical variables were obtained as well as measures of central tendency (mean) and dispersion (standard deviation) of the numerical variables.

To verify the possible differences in clinical and socio-demographic characteristics between the two groups (SA and non-SA), the chi-square test and Student's *t*-tests were used when appropriate. After this initial analysis, the variables that showed a more significant difference ($p < 0.20$) between the two groups were adjusted in the multivariate regression, apart from religious affiliation, seeing as it is also a religious variable.

In the bivariate analysis, the measure of association (odds ratio [OR]) was estimated using a logistic regression model with a respective confidence interval (CI) of 95% between the religiosity domains (ORA, NORA, and IR) and the outcome variable (suicide attempts). By using a multivariate logistic regression, an adjusted measure was obtained with the variables sex, employment, presence of partner, having children, psychiatric comorbidity, rapid

cycling, family history of suicide attempt or suicide, and impulsivity. The goodness-of-fit model adjustment was verified by the Akaike information coefficient statistic, and the significance level adopted for the regression analysis was 5% ($p \leq 0.05$).

3. Results

Two hundred and six patients were selected, of which 28 (13.5%) were excluded for not being euthymic, 10 (4.8%) for presenting other forms of BD, and 4 (2%) for being unable to answer the questionnaires. One hundred and sixty-four euthymic bipolar I patients were evaluated; of these, 67 (40.8%) were from the SA group and 97 (59.1%) were from the non-SA group.

Compared with the non-SA group, the SA group had more psychiatric comorbidity ($p=0.007$), more rapid cycling ($p=0.004$), and higher levels of impulsivity in all domains AI ($p=0.000$), MI ($p=0.000$), AP ($p=0.000$) and TI ($p=0.000$) and less religious affiliation ($p=0.006$). More than half of the SA group (53.7%) had a history of more than one suicide attempt throughout life. The clinical and demographic characteristics of the sample are shown in Table 1.

The comparison between the SA and non-SA groups in the multivariate analysis, after controlling for gender, employment, presence of partner, having children, psychiatric comorbidity, rapid cycling, family history of suicide attempt, family history of suicide, and impulsivity domains, showed a protective effect of NORA (OR, 0.66; 95% CI, 0.50–0.86) and IR (OR, 0.70; 95% CI, 0.60–0.81). In ORA, the difference was not significant (OR, 0.85; 95% CI, 0.67–1.06) (Table 2).

Table 1
Demographic and clinical characteristics of participants.

Variables	Non SA (n=97) N (%)	SA(n=67) N (%)	p^*
Age, mean (SD), years	43.80 (12.74)	41.73 (11.04)	0.281
Sex, female	75 (77.3%)	44 (65.7%)	0.100
Employed	32 (33%)	14 (20.9%)	0.090
Has partner	36 (37.1%)	33 (49.3%)	0.122
Has children	53 (54.64%)	44 (65.67%)	0.158
Has religious affiliation	86 (88.7%)	48 (71.6%)	0.006
Catholic	43 (44.3%)	17 (25.3%)	
Protestant	36 (37.1%)	25 (37.3%)	
Spiritism doctrine	6 (6.1%)	6 (8.9%)	
Afro-Brazilian religions	1 (1.0%)	0 (0.0%)	
Lifetime psychiatric comorbidities	18 (18.6%)	25 (37.3%)	0.007
Lifetime psychosis	58 (59.79%)	41 (61.19%)	0.972
Family history of suicide attempt	14 (14.4%)	13 (19.4%)	0.164
Family history of suicide	20 (20.62%)	15 (22.39%)	0.149
Lifetime hospitalization	66 (68.0%)	47 (70.1%)	0.774
Lifetime using of lithium	81 (83.51%)	53 (79.1%)	0.295
Length of illness mean (SD), years	16.22 (11.08)	17.66 (17.66)	0.429
Rapid cycling	18 (18.6%)	25 (37.3%)	0.004
Polarity predominance			0.223
Positive	52 (53.61%)	26 (38.8%)	
Negative	23 (23.71%)	21 (31.34%)	
Without	19 (19.59%)	15 (22.39%)	
Unknown	3 (3.09%)	5 (7.46%)	
Impulsiveness mean (SD)			
Attentional	18.007 (3.32)	21.298 (4.26)	0.000
Motor	20.000 (5.17)	23.716 (6.77)	0.000
Planning	23.206 (5.75)	27.626 (6.22)	0.000
Total	61.214 (11.56)	72.641 (15.03)	0.000

SD=standart deviation, SA=suicide attempters,

* Chi square or Student's t-test.

Table 2
Religiosity and suicide attempts in bipolar I patients.

Variables	Bivariate analysis			Multivariate analysis*			
	OR	P	IC 95%	OR	P	IC 95%	
ORA	0.76	0.007	(0.63–0.92)	ORA	0.85	0.160	(0.67–1.06)
NORA	0.63	0.000	(0.49–0.75)	NORA	0.66	0.002	(0.50–0.86)
IR	0.68	0.000	(0.59–0.77)	IR	0.70	0.000	(0.60–0.81)

ORA=Organizational religious activities; NORA=No Organizational religious activities, IR=Intrinsic religiosity; OR=odds ratio; IC=Intervals Confidence

* Adjusted for impulsiveness and clinical-socio-demographic variables.

4. Discussion

To the best of our knowledge, this is the first study with the main objective of evaluating the relationship between religiosity and SB in bipolar I outpatients who were evaluated only in a euthymic state using strict criteria. In this study, we found that higher scores of NORA and IR were inversely related to a history of suicide attempts, even when controlling for variables that might also interfere with SB, such as rapid cycling and the presence of comorbidities. As expected, a higher frequency of psychiatric comorbidities and rapid cycling were found in the SA group compared with the non-SA group; these factors are related to a greater risk of SB (Malhi et al., 2013; Oquendo et al., 2010; Garcia-Amador et al., 2009).

Another important point is in relation to religious affiliation. Patients in the non-SA group were more affiliated with a religion than those in the SA group. In this regard, it is generally known that individuals who ascribe to any type of religion are less tolerant of SB than those who ascribe to no religion at all (Koenig et al., 2001). The same results were described in a study that evaluated bipolar patients in a depressive phase that found less history of SB in patients with a religious affiliation compared with those with no religious affiliation (Dervic et al., 2011). In this study, the likely mediator is a greater moral objection to SB in those with a religious affiliation than in those without such an affiliation. However, other findings have demonstrated that religious involvement is more important than simple religious affiliation, emphasizing the way in which an individual lives out his/her religiosity and spirituality regardless of whether he/she is a follower of a specific religion. This level of religious involvement could vary among people of the same religion or even among those with no specific religious affiliation (Moreira-Almeida et al., 2006; Koenig et al., 2001).

In our study, we also found that the SA group showed higher levels of impulsivity in all domains of BIS-11 in relation to the non-SA group. Furthermore, when analyzed separately, the mean overall score of this scale was higher than 72 points, which translates to a high level of impulsivity in the SA group (Stanford et al., 2009). These data confirm results from studies that have shown a positive relationship between greater impulsivity and SB (Mahon et al., 2012). In fact, a recent review showed that impulsivity is significantly higher in remitted bipolar patients than in normal controls, suggesting that elevated impulsivity is one of the characteristics of patients with BD who are also in a state of euthymia (Saddichha and Schuetz, 2014).

The multiple links that have been established between higher levels of impulsivity and SB have still not been completely clarified (Anestis et al., 2014; Watkins and Meyer, 2013), but impulsivity may worsen the course of the illness by contributing to substance abuse, non-adherence to treatment and, consequently, more SB (Mahon et al., 2012; Swann et al., 2004, 2009; Michaelis et al., 2004). Within this line of research, factors that might interfere in the relationship between impulsivity and SB, such as religiosity and resilience, must be studied further (Caribé et al., 2015; Choi

et al., 2015). In fact, despite the association between rapid cycling, psychiatric comorbidity, and impulsivity with suicide attempts, our results showed a protective effect of religiosity in relation to SB in the non-SA group. Nonetheless, this effect was significant only in relation to the NORA and IR domains.

To better understand the results of this research, it is worth noting that the patients evaluated were euthymic under strict criteria so that we could record their religious experiences in a more stable manner and without possible distortions caused by mood changes, which often occur in BD. Research shows that, due to the characteristics of mood elation, bipolar patients may undergo more conversion, salvation and mystical experiences in addition to greater religious involvement than those with other mental illnesses or healthy subjects (Stroppa and Moreira-Almeida 2009; Soeiro et al., 2008). Similarly, depressive states have been found to have an inverse relationship with religiosity (Stroppa and Moreira-Almeida, 2013; Smith et al., 2003). A study conducted with 334 BD outpatients found that rates of prayer/meditation were higher among those in a mixed state and lower among euthymic BD patients. Depressive and manic states did not correlate with any of the measured dimensions of religiosity. The authors suggested that the greater severity and worse prognosis of mixed states may be reasons for an increase in the frequency of private religiosity behavior as a coping strategy (Cruz et al., 2010). Nonetheless, the way that religiosity and spirituality dimensions change with mood swings is poorly understood (Aubin, 2010).

In contrast to our results that religiosity protects the bipolar patient with regard to SB, a study that compared depressive patients with Low Religious Involvement (LRI) with those with High Religious Involvement (HRI) concluded that in these patients, HRI associated with mixed features may increase the risk of SB despite the existence of religious affiliation (Azorin et al., 2013). The authors also suggested that in these cases, it is likely that religious involvement may aggravate feelings of guilt or the sinful character of their hypomanic experiences, thereby enhancing suicidal tendencies. However, it is important to note that in this study, the authors included a heterogeneous sample comprising unipolar and depressive bipolar spectrum patients who had either spontaneous or antidepressant-associated hypomania. Moreover, the measure of religiosity could have generated bias at the cut-off point for LRI and HRI because the DRI scale was evaluated on the total score without taking into account its three dimensions (ORA, NORA, and IR) separately, which is not recommended by the authors of the scale (Koenig et al., 1997; Lucchetti et al., 2012).

Regarding the analysis of religiosity dimensions, after the multivariate analysis, ORA failed to maintain a protective effect in relation to SB. Organizational religious activities reflect the social aspects of religiosity and have proven to be relevant to health outcomes in that belonging to a religious group can provide support in times of stress and suffering (Hovey et al., 2014). However, the protective effect of religiosity does not seem to be caused solely by social contact established among participants (Rasic et al., 2009). In fact, some studies show that positive effects of religiosity remain even after controlling for the social support that is offered by most religions (Nisbet et al., 2000; Corrêa et al., 2011; Harvey et al., 2015).

Another factor revealed in previous research is that people who have better physical and mental health tend to attend religious meetings more often than others (George et al., 2002; Corrêa et al., 2011). Thus, bipolar patients, who frequently experience symptoms of illness, are prevented from maintaining their daily activities, including attending church or other religious centers. Hence, in this study, the sample of subjects with a serious illness such as BD may indicate the presence of several social limitations and reduced attendance at religious meetings, although this may not necessarily indicate diminished religiosity in other aspects, such as

NORA and IR.

Another issue related to less frequent attendance at religious meetings is the secularization process that has been ongoing in Western countries over the past few centuries. Increasingly, religious experience does not depend on regulation from institutions, causing it to be more subjective and less formal. In fact, NORA involve the private practice of prayer, meditation, or readings independent of institutions or specific liturgy (Koenig, 2009).

In our study, NORA presented as a protective factor for SB even after controlling for confounding variables, which confirms previous studies that showed an inverse relationship between NORA and SB (Caribé et al., 2012; Nonnemaker et al., 2003), as well as a positive association between more NORA and mental health, mainly if the subject believes that prayer is beneficial and does not carry out the act of praying automatically or due to obsessive compulsive symptoms (Pössel et al., 2014; Bonchek and Greenberg, 2009).

In a cross-sectional study of 81 individuals with BD, 78% reported having religious beliefs, and 81% reported involvement in religious activities. Those who had not felt well in the previous five years mentioned that private religious practice had helped them to cope with their disease, indicating that NORA might be used as a coping strategy with regard to the illness (Mitchell and Romans, 2003). Another important point is that studies using positron emission tomography (PET-SCAN) revealed that religious practice stimulates the limbic system, increasing the activity of the autonomic centers of the nervous system, such as the hypothalamus, amygdala, and hippocampus. Additionally, religious practice promotes increased prefrontal cortex metabolism that in turn influences impulse control, decision-making, and moral judgments (Seybold, 2007; Newberg et al., 2001). There is evidence that NORA practice could have positive repercussions on mental health, impulsivity, and SB, although caution is necessary when affirming this suggestion regarding bipolar patients.

The IR domain measures the integration of religiosity in the life of the individual and attempts to capture the extent to which the person is internally committed to his/her religion. Positive outcomes in mental health have been reported whether IR is evaluated separately or combined with other aspects of religiosity (Mosqueiro et al., 2015; Power and McKinney, 2014). In our study, greater IR showed a negative association with SB. In a recent study, it was shown that greater IR was associated with fewer depressive symptoms and better quality of life (QOL) in bipolar patients (Stroppa and Moreira-Almeida, 2013). However, more depressive symptoms and lower QOL have been associated with SB in these patients (Ryu et al., 2010; Abreu et al., 2012). Therefore, higher IR may influence these relations and act as a protective mechanism against SB, as found in our research.

Our study encountered some limitations: a small sample size, the cross-sectional design that precluded the possibility of assessing cause and effect relationships, and the infeasibility of determining the time lapse between the last suicide attempt and the period when the patients were evaluated. Also, it was not possible to control possible changes in patients' religious experience after a suicide attempt. Furthermore, we do not have at our disposal the total number of patients assisted at the respective centers, or the sociodemographic data relating to the excluded population. Therefore, caution is suggested in generalizing these results.

5. Conclusions

Our results showed that even after controlling for important variables, such as the presence of psychiatric comorbidities, rapid cycling and high levels of impulsivity, NORA and IR maintained an inverse relationship with SB in BD I patients. Further exploration

of the relationship between religiosity and BD may increase our understanding of this connection and minimize the suffering and disabilities linked to BD.

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4.3 ARTIGO Nº 3: SYSTEMIC LUPUS, FOLIE A TROIS AND HOMICIDE

Systemic lupus, folie a trois and homicide

Publicado na revista: **Comprehensive Psychiatry**

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Systemic lupus, folie a trois and homicide

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Abstract

Folie a trois is a syndrome characterized by the transfer of delusional ideas from one person to two other persons. This condition rarely ends in the murder of any involved and we are unaware of where the primary case had the diagnosis of acute psychosis in systemic lupus erythematosus (SLE). We present a case report of folie a trois resulting in murder, secondary to acute psychosis in SLE.

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1. Introduction

Shared psychosis, *folie a deux*, is a rare condition described for the first time in 1877 by Lasègue and Falret. The syndrome is characterized by a transfer of delusions and abnormal behaviors from one person to others. The delusions are shared by two or more, closely related, socially isolated, people, usually family members [1]. The primary case often has diagnosed schizophrenia, delusional disorder or mood disorder with psychotic features [2]. The secondary case is characteristically younger, has a passive personality or shows mental retardation [3].

2. Case report

Patient AR, a 50-year-old married mother of six, described as centralizing and domineering personality in family relationships, without history of previous psychiatric disease, was arrested in her town, along with her youngest son, DS, and sent to a psychiatric hospital, after murdering her oldest son, AB.

Thirty days before the crime, she presented a two-day episode of agitation and incomprehensible speech. The episode was self-limited and the patient could not explain what had happened. Eleven days before the crime, her younger daughter returned to the city presenting maniac and psychotic symptoms after childbirth. The family believed it was some kind of “spiritual obsession” and solicited local healers. Another local religious group, knowing the situation, imposed uninterrupted sessions of exorcism in her daughter. The entire situation resulted in stress and sleep deprivation for the family.

Seven days before the crime, AR showed changes in behavior inconsistent with social and religious customs of the family. She presented soliloquy, agitation, visual and auditory hallucinations, religious sayings and references to the devil. Four days before the crime, three days after AR symptoms, DS, her younger son, mentally retarded and emotionally dependent on her, developed the same symptoms. AR said the household objects were moving and fragmenting in her hand, saw people resembling goats, local reference for devils, confirmed by DS. Two days before, AB returned home, for 3 h, holding DS and AR, praying aloud. AB started to behave like his brother and mother, and one day before the crime, they tried to kill their father, AR’s husband, after her accusation that he had goat legs and ears, therefore replaced by the devil. Wounded, he managed to escape. During the night, while they slept, AR began hearing voices, seeing shadows, and identified a half-human, half-animal being. They started fighting in the dark. AR only

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remembers the day dawning, a creature on the ground, dead. DS saw the same creature, and left home to seek help. Shortly after, the father returned home to see his oldest son killed, strangled with wire. He found his wife bloodied and angry, and she told him a goat-faced demon had invaded the house, which she had to kill to defend the family. She did not recognize her son.

Mother and son were conducted to local hospital, maintaining the symptoms and hospitalized for one month, treated with haloperidol, chlorpromazine, mechanical restraints and injectable haloperidol when necessary. They were admitted to the psychiatric hospital two months later without any medication. AR was oriented, collaborative, thought organized, no changes in sensory perception, depressed mood, aware of the facts, but using spiritual justification for her actions. She argued that she would never kill her son and believed she was possessed. DS was also aware, but with childish behavior, difficulty with abstracting, interpreting the facts in a religious context. An acute psychotic disorder was diagnosed for AR, mental retardation for DS, and a shared psychotic disorder for both. Both were considered legally exempt from punishment.

In the hospital, DS was separated from his mother and treated with clonazepam. He evolved without symptoms and was followed as an outpatient. In the following months, AR evolved with short, intermittent episodes of agitation, slurred speech with mystical content that improved with use of antipsychotics. After, she presented asthenia, decreased muscle strength in legs, knee and right wrist arthritis, constipation, abdominal pain, malar rash and fever. The laboratory presented antinuclear antibody (ANA) positive 1:160 (mixed pattern: nuclear fine speckled and homogeneous), PCR = 6.35, Hemoglobin = 8.0, Platelets = 100,000. The patient developed seizures and died with diagnosis (SLE).

3. Discussion

According to our knowledge, this is the first case of *folie a trois* where the primary patient is diagnosed with SLE with psychotic features. This case stands out because of the rare and unexpected disorders developed by the patients. Psychotic disorders, including the Schizophrenia spectrum that accounts for approximately two-thirds of all psychotic disorders, usually onset between 15 and 35 years [4]. Regarding the shared psychotic disorder, various features of the case fit the descriptions found in the literature, having international classifications DSM-IV and ICD-10, albeit with no clear evidence of social isolation in this case. Despite the presence of this feature in the first descriptions of *folie a deux*, this is not included in DSM-IV and ICD-10 as a

criterion. However, Silveira and Seeman found revising published case reports between 1942 and 1993, where social isolation is a frequent feature in these cases [5].

In this family, we observed a strong influence of local religious culture. Even after the mother's death, due to a confirmed disease, all family members continued to contextualize the phenomena through a mystical and religious understanding. The existence of a plethora of cultural belief systems sometimes makes distinguishing cultural beliefs from delusions a difficult task. Cultures are complex and symbolic systems, and awareness of that specific culture is important in gaining an understanding of an individual [6].

SLE is an autoimmune disease that onsets more frequently in adolescents and young adults [7]. Although psychosis is one of the most severe psychiatric manifestations in SLE, it is a rare disease manifestation with low prevalence, ranging from 0% to 11% [7]. Furthermore, psychosis as the first symptom of SLE is even rarer: in a sample of 458 patients, Pego-Reigosa et al. found only six where psychotic symptoms occurred as initial presentation of SLE [8].

Although a systematic search for ANA in all psychotic patients is of little use, as presented by Hopkinson et al. [9], in this case it could have been suitable. With atypical age of onset for psychotic disorder, the acute nature of the symptoms and the presence of vivid visual hallucinations, one must raise the question of and investigate the possibility of organic diseases.

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5 CONCLUSÕES

1. A religiosidade/espiritualidade pode alterar o prognóstico dos transtornos de humor.
2. A presença da doença mental pode interferir na relação entre a religiosidade, a impulsividade e o comportamento suicida.
3. A impulsividade pode ser um mediador entre maiores níveis de religiosidade e menor CS.
4. A religiosidade não organizacional (RNO) e a intrínseca (RI) atuaram como mecanismo de proteção ao CS em portadores de TB tipo I, avaliados em estado de eutimia.
5. A vivência religiosa dos indivíduos e sua imersão cultural podem interferir na manifestação psicopatológica de quadros psicóticos.

6 CONSIDERAÇÕES FINAIS

A relação do homem com a religiosidade é bastante antiga e de diversas maneiras interferiu na expressão do seu comportamento. Dessa forma, a busca por uma compreensão melhor entre as complexas relações que se estabelecem entre R/E e doença mental são de fundamental importância para a melhor prática psiquiátrica. Sabe-se que a vivência religiosa é algo relevante para a maioria dos indivíduos em diversas culturas e os profissionais da área de saúde não devem ignorar este aspecto.

A R/E e suas relações culturais podem estabelecer limites muito tênues entre o normal e o patológico. Mais ainda, a R/E, através de múltiplos mecanismos, podem atuar como ferramenta de enfrentamento para as doenças mentais, modificando graves desfechos, tais como o suicídio. Neste sentido, um ponto importante também será o desenvolvimento de melhor compreensão dos fatores de mediação entre R/E e saúde mental, assim como as possíveis aplicações deste conhecimento na prática clínica de modo mais sistematizado.

Esta pesquisa traz pontos importantes e alerta sobre o papel da R/E na saúde mental, avaliados através de instrumento específico. Entretanto, apresenta algumas limitações. Devido aos desenhos dos estudos, não foi possível estabelecer-se uma relação de causa e efeito entre os resultados. Em relação ao CS, não foi possível controlar possíveis mudanças no padrão da vivência religiosa dos indivíduos antes e após as tentativas de suicídio.

7 PERSPECTIVAS DE ESTUDOS

- Ampliar os estudos em pacientes com TB e com outras patologias que apresentam risco de suicídio, avaliando possíveis mediadores entre a religiosidade e a doença mental, incluindo também os transtornos de personalidade.

- Estudar o papel do apoio social na relação entre transtorno bipolar e religiosidade.

- Investigar as relações entre a religiosidade e suas repercussões em portadores de hepatite C e do vírus HTLV.

ANEXO A – PARECER DO COMITÊ DE ÉTICA

COMITÊ DE ÉTICA EM PESQUISA – CEP/MCO/UFBA
MATERNIDADE CLIMÉRIO DE OLIVEIRA
UNIVERSIDADE FEDERAL DA BAHIA

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PARECER/RESOLUÇÃO N.º 16/2005.

Registro CEP: 16/2005 – 17.02.2005.

Projeto de Pesquisa: "Programa da Avaliação Continuada do Centro de Estudos e Tratamento dos Transtornos Afetivos (TA) do HUPES"

Pesquisadora Responsável: Doutora, **Ângela Marisa de Aquino Miranda-Scippa**, Professora Adjunta da FAMEB. **Pesquisadoras Auxiliares:** **Fabiana Nery Fernandes**, Médica Residente e **Amanda Cristina Galvão Oliveira de Almeida**, Médica com Especialização em Psiquiatria. "*Curricula vitae*" em anexos.

Patrocínio: Recursos próprios — Grupo de Pesquisa em Psiquiatria do HUPES.

Instituição: Hospital Universitário Professor Edgar Santos (HUPES) — Universidade Federal da Bahia.

Área do conhecimento: 4.01, Nível E, Grupo III.

Objetivos: **geral** — descrever as características clínicas e demográficas dos pacientes com transtorno afetivo, em um Centro de atendimento terciário em Salvador-Bahia e **específicos** — determinar a prevalência de co-morbidades psiquiátricas do eixo I em pacientes com transtorno afetivo bipolar (**TAB**), segundo os critérios do DSM-IV; descrever as características clínicas e demográficas dos pacientes com transtorno afetivo bipolar portadores e não-portadores de co-morbidade psiquiátrica; avaliar possíveis diferenças entre os portadores de transtorno afetivo bipolar com e sem co-morbidade psiquiátrica, em relação à qualidade de vida.



**COMITE DE ETICA EM PESQUISA – CEP/MCO/UFBA
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Sumário: Pacientes com **TAS/DSM-IV** do **CETTA**, com idade ≥ 18 anos, serão incluídos. **Protocolo** elaborado, (anexo), e **"Entrevista Clínica Estruturada"**, (com base em múltiplas **"escalas"** e procedimentos investigatórios), além do **"Livro do Avaliador"**, compõem o complexo, extenso e minucioso procedimento investigatório e de avaliação a ser utilizado. Estudo de corte transversal com aplicação feita simultaneamente por dois investigadores, inclusive com familiares se necessário. Autônomos, Centros em Pelotas e Porto Alegre, (Universitários) também realizarão o estudo, sobre um total aproximado de 600 pacientes. **Cronograma** incluso. Procedimentos estatísticos descritos. Bibliografia pertinente.

Comentários: A fundamentação teórica, sintética, mas bem explicitada suporta a realização da pesquisa, máxime considerando que este estudo foi pouco efetuado no Brasil, com sua maioria em São Paulo e Porto Alegre. A miscigenação humana local o recomenda e o relato das co-morbidades interferentes na qualidade de vida não foi bem avaliada no país. O **"Termo de Consentimento Livre e Pré-Esclarecido"** é ético. **Proposição aprovável.**

Salvador, 23 de Fevereiro de 2005.

Decisão Plenária: *Aprovado*

Coordenador: *Dr. Antonio dos Santos Barros*

Observação importante: toda a documentação anexa ao Protocolo proposto e rubricada pela Pesquisadora, arquivada neste CEP, e também a outra devolvida com a rubrica da Secretária deste à mesma, faz parte intrínseca deste Parecer/Resolução.



COMITÊ DE ÉTICA EM PESQUISA – CEP/MCO/UFBA
MATERNIDADE CLIMÉRIO DE OLIVEIRA
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IORG0003460. Assurance FWA00002471, October 26, 2010
IRB00004123, October 5, 2007 - October 4, 2010

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PARECER/RESOLUÇÃO ADITIVA N.º 159/2010

Para análise e deliberação deste Colegiado a Professora, Doutora, **Ângela Marisa de Aquino Miranda-Scippa**, Pesquisadora Responsável pelo Projeto de Pesquisa: **“Programa da Avaliação Continuada do Centro de Estudos e Tratamento dos Transtornos Afetivos (CETTA) do HUPES”**, aprovado em 23 de Fevereiro de 2005 pelo Parecer/Resolução N.º 16/2005 deste Institucional, encaminhou, em 28 de junho de 2010, o **“SCID-II — Entrevista Clínica Estruturada para transtornos de personalidade do Eixo II do DSM-IV”, Versão Brasileira 1.0 (Setembro/2008); “Escala de Religiosidade da Universidade de Duke —DUREL”;** **“Escala de Experiência Sexual (ASEX) e o “Questionário de Suporte Social—SSQ”.**

Inexistindo na proposição analisada conflito administrativo, processual e ético que contra-indiquem as incorporações pretendidas e a conseqüente continuidade executória local do Estudo, fica a mesma **aprovada** por este Institucional.

Salvador, 14 de julho de 2010

Professor, Doutor, Eduardo Martins Netto,
Coordenador em Exercício – CEP/MCO/UFBA

Observações importantes. Toda a documentação anexa ao Protocolo proposto e rubricada pelo (a) Pesquisador (a), arquivada neste CEP, e também a outra devolvida com a rubrica da Secretária deste (a) ao (à) mesmo (a), faz parte intrínseca deste Parecer/Resolução e nas “Recomendações Adicionais” apenas, **bem como a impostergável entrega de relatórios parciais e final como consta nesta liberação**, (Modelo de Redação para Relatório de Pesquisa, anexo).

ANEXO B – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E PRÉ-ESCLARECIDO
PROGRAMA DE AVALIAÇÃO CONTINUADA DO CENTRO DE ESTUDOS E
TRATAMENTO DOS TRANSTORNOS AFETIVOS DO HUPES

Nome e número do estudo:

Nome do paciente:

Data de nascimento:

Médico avaliador:

Médico supervisor:

Número do protocolo:

Número do prontuário:

Antes de participar deste estudo, gostaríamos que você tomasse conhecimento do que ele envolve. Damos abaixo alguns esclarecimentos sobre dúvidas que você possa ter. Em caso de qualquer outra dúvida quanto ao estudo e o que ele envolve e sobre os seus direitos, você deverá contatar a Dra. Ângela Scippa pelo telefone (71) 332-3509, segundas-feiras pela manhã ou o Coordenador do Comitê de Ética em Pesquisa, pelo telefone (71) 203-2740, ou no Ambulatório Magalhães Neto.

Qual o objetivo desta pesquisa?

Conhecer as características clínicas dos pacientes em atendimento no Centro de Estudos e Tratamento dos Transtornos Afetivos (CETTA) do Hospital Universitário Professor Edgard Santos (HUPES), bem como avaliar a qualidade do tratamento médico e a qualidade de vida dos pacientes.

O que acontecerá neste estudo?

Os pacientes responderão às questões em estudo através de questionários que determinam a presença de diferentes doenças psiquiátricas, a intensidade do transtorno afetivo e a qualidade de vida dos pacientes. A aplicação destas escalas terá uma duração de duas a três consultas. Os investigadores não estarão sendo remunerados para a realização desse estudo, assim como os pacientes voluntários não receberão benefícios financeiros para a sua participação no mesmo.

Quais os benefícios em participar deste estudo?

A sua participação neste estudo poderá proporcionar, no âmbito pessoal, a identificação de algum problema não antes conhecido, sendo assim tratado de maneira mais específica e adequada, e no âmbito coletivo, poderá ajudar no desenvolvimento de um melhor plano de atendimento aos demais pacientes.

Quais os direitos dos participantes?

Os pesquisadores deste estudo podem precisar examinar os seus registros, a fim de verificar as informações para o objetivo deste estudo. No entanto, os seus

registros médicos serão sempre tratados confidencialmente. Os resultados deste estudo poderão ser enviados para publicação em jornal científico, mas você não será identificado por nome. Sua participação no estudo é voluntária, de forma que caso você decida não participar, isto não afetará o tratamento normal ao qual você tem direito.

Quais são as responsabilidades dos participantes?

Os participantes deste estudo comprometem-se a comparecer às consultas marcadas, bem como responder fidedignamente as escalas aplicadas pelos médicos pesquisadores e as escalas auto-aplicáveis.

1. Recebi uma explicação completa do objetivo do estudo, dos procedimentos envolvidos e o que se espera da minha pessoa.

2. Estou ciente de que tenho total liberdade de desistir do estudo a qualquer momento e que esta desistência não irá, de forma alguma, afetar meu tratamento ou administração médica futura na instituição.

3. Estou ciente de que a informação nos meus registros médicos é essencial para a avaliação dos resultados do estudo. Concordo em liberar esta informação sob o entendimento de que ela será tratada confidencialmente, ou seja, não serei referido por nome em qualquer relatório relacionado a este estudo. Da minha parte, não devo restringir, de forma alguma, o uso dos resultados que possam surgir no estudo.

4. Concordo total e voluntariamente em fazer parte deste estudo; tenho mais de 18 anos.

5. Como tenho dificuldade para ler (sim ___ ou não ___), o escrito acima, atesto também que o(a) Dr.(a) _____ quando da leitura pausada desse documento, esclareceu todas minhas dúvidas e como dou minha concordância para participar do estudo, coloco abaixo a impressão do meu dedo polegar.

Assinatura do paciente: _____

Data: _____

Assinatura do médico avaliador: _____

Data: _____

Assinatura do familiar responsável pelo paciente: _____

Data: _____

ANEXO C – Outros Artigos Nº 1: Clinical characteristics and the influence of history of childhood trauma on the prodrome of bipolar disorder

CLINICAL CHARACTERISTICS AND THE INFLUENCE OF HISTORY OF CHILDHOOD TRAUMA ON THE PRODROME OF BIPOLAR DISORDER

Publicado na: Revista Brasileira de Psiquiatria

ORIGINAL ARTICLE

Clinical characteristics and influence of childhood trauma on the prodrome of bipolar disorder

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Objectives: To describe the onset pattern, frequency, and severity of the signs and symptoms of the prodrome of the first hypomanic/manic episode and first depressive episode of bipolar disorder (BD) and to investigate the influence of a history of childhood maltreatment on the expression of prodromal symptoms.

Methods: Using a semi-structured interview, the Bipolar Prodrome Symptom Scale-Retrospective (BPSS-R), information regarding prodromal symptoms was assessed from patients with a DSM-IV diagnosis of BD. History of childhood maltreatment was evaluated using the Childhood Trauma Questionnaire (CTQ).

Results: Forty-three individuals with stable BD were included. On average, the prodrome of mania lasted 35.8 ± 68.7 months and was predominantly subacute or insidious, with rare acute presentations. The prodrome of depression lasted 16.6 ± 23.3 months and was also predominantly subacute or insidious, with few acute presentations. The prodromal symptoms most frequently reported prior to the first hypomanic or manic episode were mood lability, depressive mood, and impatience. A history of childhood abuse and neglect was reported by 81.4% of participants. Presence of childhood maltreatment was positively associated with prodromal symptoms, including social withdrawal, decreased functioning, and anhedonia.

Conclusions: This study provides evidence of a long-lasting, symptomatic prodrome prior to first hypomanic/manic and depressive episode in BD and suggests that a history of childhood maltreatment influences the manifestations of this prodrome.

Keywords: Bipolar disorder; mania; prodrome; childhood maltreatment; depression; early stages

Introduction

Bipolar disorder (BD) is a chronic and often severe mood disorder.¹ In a large subgroup of patients, BD follows a progressive course, which can lead to structural brain damage and functional impairment.² In recent years, staging models for BD have been proposed.^{3,4} (A detailed review is available elsewhere.⁵) According to these models, the disorder starts in the "at-risk period" and progresses from the first episode to chronic and, possibly, refractory stages, putatively caused by neurobiological alterations such as an increase in neurotoxic states and reduction of neurotrophic and neuroprotective factors.^{6,7}

The progression of BD results in deterioration of clinical symptoms, cognition, and functioning, and leads to structural damage. From this perspective, prevention of BD and its early diagnosis and treatment are paramount to reducing the major economic, psychosocial, and functional impact of this disorder by delaying its onset or, perhaps, even preventing its full-blown development.^{8,9}

Clinical experience and retrospective studies have reported that the majority of individuals with BD experience mild but identifiable symptoms during childhood and adolescence.¹⁰⁻¹² The symptomatic period preceding the first manic or hypomanic episode, also called the prodrome, lasts from several weeks up to many years before full BD onset,^{3,13} and often includes sub-threshold manic symptoms, depressive symptoms, cyclothymic features, anxiety, sleep disturbances, psychotic symptoms, ADHD-like symptoms, and obsessive-compulsive symptoms.^{13,14} A systematic review reported that irritability, aggression, sleep disorders, hyperactivity, anxiety,

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and mood swings are common symptoms in the early phase of the BD prodrome (also called the "distal" prodrome).^{15,16} Over time, psychopathology progresses and symptoms usually became more specific and similar to those of full BD; this is called the "proximal" prodrome.¹⁵ A 4-year, prospective study found that 38% of children and adolescents initially diagnosed with subsyndromal BD symptoms, and 25% of those diagnosed with BD-II, transitioned to BD-I during follow-up.¹⁷ Nevertheless, few studies have investigated clinical expression of the bipolar prodrome, and the vast majority of these used either unstructured questionnaires or chart-review designs. Most failed to assess the onset pattern of the disorder and symptom severity in the prodromal period.

The majority of published studies that investigated the prodromal features of BD focused on patients with BD-I.¹⁵ Although some included patients with BD-II, there is a lack of investigations focusing on prodromal symptoms in this population. One study that evaluated the prodromal period in individuals with BD-II found that they experienced clinically significant symptoms (predominantly depressive symptoms and anxiety) at an average of more than a decade before their first major mood episode.¹⁸ Most studies combined data from the two subtypes of BD,¹⁹ thus precluding any assessment of potential differences between them. However, identifying differences in the characteristics of the prodromal period of the two BD subtypes may be useful from a prognostic perspective and to better understand the neurobiology of BD.

Environmental factors, such as childhood trauma, may influence the expression of symptoms in BD,²⁰ as well as the prodromal features of the disorder. Patients with BD exhibit higher vulnerability to traumatic events during childhood.²¹ In addition, BD seems to be a stress-sensitive disorder, with the first mood episode often being triggered by psychosocial stressors.^{21,22} Childhood trauma also appears to impact the course of the illness, being associated with earlier illness onset, an increased number of comorbidities, and suicidal behavior.^{20,23} Although childhood trauma is assumed to have an important role in the early expression of symptoms in BD, to the best of our knowledge, no studies that investigated the prodromal period of this disorder have systematically evaluated the presence of childhood trauma or its influence on the prodromal manifestations of BD.

Therefore, the aim of this study was to describe the onset pattern, frequency, and severity of the signs and symptoms of the prodrome to the first depressive and the first hypomanic or manic episode of BD, using a semi-structured interview (the Bipolar Prodrome Symptom Scale-Retrospective, BPSS-R), and to compare the prodromal features of BD-I with those of BD-II. Furthermore, we sought to explore the influence of demographic and clinical variables, including history of childhood maltreatment, on the expression of prodromal symptoms. We hypothesized that: a) the prodrome to the first depressive episode would be longer than the prodrome to the first manic episode; b) there would be no significant differences between BD-I and BD-II regarding the depressive

prodrome, but the hypomanic/manic prodrome would be shorter and more symptomatic in patients with BD-I; and c) a history of childhood trauma would be associated with a greater frequency of certain prodromal symptoms, as well as with a longer prodrome duration.

Methods

This study protocol was approved by the Ethics Committee of Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil, and all individuals provided written informed consent before inclusion.

Population

Forty-three stable outpatients with BD-I or BD-II of no longer than 9 years' duration were included. The diagnosis was established in accordance with the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Clinical stability was defined as a 17-item Hamilton Depression Rating Scale (HDRS) score < 14 and a Young Mania Rating Scale (YMRS) score < 8. The exclusion criteria were presence of neurological/organic disease, inferred mental retardation, illiteracy, dementia, and current moderate or severe mood symptoms (see above).

Outcomes

The primary outcome measures were the duration of the prodrome before the first manic episode, the duration of the prodrome before the first depressive episode, and the frequency of specific prodromal symptoms. The secondary outcomes were the frequency of childhood trauma and its relationship to prodromal patterns, as well as the influence of BD subtype (BD-I vs. BD-II) on prodromal patterns.

Assessment instruments

Prodromal symptoms were evaluated by a trained psychiatrist using the Brazilian Portuguese version of the BPSS-R,^{11,24} a semi-structured interview that assesses 36 signs and symptoms that emerge or worsen prior to the first depressive or manic episode. It investigates all DSM-IV symptoms of mania and depression, psychotic symptoms, and general psychopathology, and assesses not only the presence of symptoms, but also their onset pattern, duration, severity, frequency, and possible association with substance abuse. Prodromal symptom severity is rated as 1 = mild, 2 = moderate, or 3 = severe. Symptom frequency is rated as 1 = infrequent, 2 = recurrent, 3 = very frequent, or 4 = static lifetime or character trait. Consistent with conventions used for the psychotic prodrome,²⁵ symptoms were included in the analysis if they were of at least moderate severity and were not considered a character trait, unless the severity had increased by at least one point before the onset of the disorder. Regarding onset pattern, the prodrome was classified as acute (< 1 month in duration), subacute (1-12 months in duration), or

insidious (> 1 year in duration).¹¹ Prodromal symptoms that emerged prior to the first depressive or manic/hypomanic episode were systematically investigated through retrospective patient reports.

Childhood maltreatment was assessed using a translated and validated version of the Childhood Trauma Questionnaire (CTQ).^{26,27} This is a self-report instrument used to document history of childhood maltreatment in five domains: sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. The instrument consists of 28 questions and the severity of trauma is graded on a five-point Likert-type scale, from absent to severe. Childhood trauma is classified as none, low, moderate, or severe. For purposes of analysis, a history of trauma was classified dichotomously as absent (patients who experienced no or minimal trauma) or present (patients who experienced low, moderate, or severe trauma during childhood and adolescence).

Depressive and manic symptom severity was assessed using the HDRS and YMRS²⁸ respectively. Illness severity was assessed using the Clinical Global Impressions-Severity

(CGI-S) scale, and global functioning, using the Global Assessment of Functioning (GAF) scale.

Statistical analysis

Data were tabulated and analyzed in SPSS version 20.0 for Mac. Descriptive statistics included mean and standard deviation or median and percentiles and percentage, as appropriate. Between-group differences (i.e., prodrome to first depressive vs. first hypomanic/manic episode; BD-I vs. BD-II; patients with vs. without childhood trauma) were analyzed using the chi-square and Student's *t* test. All tests were two-tailed and statistical significance was set at ≤ 0.05 . Due to the exploratory nature of the analyses, no adjustment for multiple testing was made.

Results

Clinical and demographic characteristics

The clinical and demographic characteristics of the sample are described in Table 1. Altogether, 43 stable

Table 1 Sociodemographic and clinical characteristics of the sample

Variable	Total (n=43)	BD-I (n=32)	BD-II (n=11)	p-value
Age (years), mean (SD)	33.7 (8.0)	34.1 (8.9)	32.7 (9.0)	0.664
Sex (female), n (%)	32 (74.4)	26 (81.3)	6 (54.5)	0.080
Years of education, mean (SD)	11.1 (2.6)	10.6 (2.4)	12.7 (2.6)	0.028
Age (years) at first mood episode, mean (SD)	25.3 (8.1)	26.7 (8.3)	21.2 (5.6)	0.046
Polarity of first mood episode, n (%)				
Depressive	22 (51.1)	14 (43.8)	8 (72.7)	0.097
Manic	14 (32.5)	14 (43.8)	0 (0.0)	0.037
Mixed	5 (11.6)	4 (12.5)	1 (9.1)	0.761
Hypomanic	2 (4.6)	0 (0.0)	2 (18.2)	0.084
Duration of illness (years), mean (SD)	8.5 (7.3)	7.7 (6.2)	10.6 (9.8)	0.267
Years since BD diagnosis, mean (SD)	10.5 (7.5)	10.7 (5.6)	10.0 (9.9)	0.842
Number of mood episodes until an episode of the opposite polarity, mean (SD)	1.7 (2.3)	0.9 (0.8)	3.7 (3.7)	0.038
Number of mood episodes, median (IQR)	4.0 (2.0-9.0)	4.0 (2.0-5.0)	10 (5.0-10.0)	0.035
Number of hypomanic/manic episodes, median (IQR)	3.0 (2.5)	2.7 (2.5)	3.6 (2.7)	0.339
Number of depressive episodes, median (IQR)	2.9 (3.1)	2.2 (2.9)	4.7 (3.1)	0.024
Comorbidity with substance use disorders, n (%)				
Alcohol abuse	2 (4.7)	0 (0.0)	2 (18.2)	0.014
Alcohol dependence	1 (2.3)	0 (0.0)	1 (9.1)	0.084
Illicit drug abuse/dependence	3 (6.9)	1 (3.1)	2 (18.2)	0.091
History of suicide attempt, n (%)	10 (23.3)	8 (25.0)	2 (18.2)	0.189
History of hospitalization, n (%)	18 (41.9)	15 (46.9)	3 (27.3)	0.256
Lifetime history of psychotic symptoms, n (%)	26 (60.5)	24 (75.0)	2 (18.2)	0.001
First-degree relative with BD, n (%)	7 (16.3)	2 (6.3)	5 (45.5)	0.008
HDRS score, mean (SD)	3.4 (4.1)	3.1 (3.8)	4.3 (5.0)	0.401
YMRS score, mean (SD)	0.8 (1.5)	0.6 (1.2)	1.2 (2.0)	0.344
GAF score, mean (SD)	78.5 (13.2)	78.4 (13.4)	78.7 (13.3)	0.951
CGI score, mean (SD)	1.6 (0.8)	1.7 (0.8)	1.8 (1.1)	0.589
History of childhood maltreatment, n (%)				
Emotional abuse	25 (58.1)	22 (68.8)	3 (27.3)	0.016
Physical abuse	13 (30.2)	10 (31.3)	3 (27.3)	0.804
Sexual abuse	12 (27.9)	11 (34.4)	1 (9.1)	0.107
Physical neglect	21 (48.8)	19 (59.4)	2 (18.2)	0.018
Emotional neglect	21 (48.8)	16 (50.0)	5 (45.5)	0.795
At least one modality	35 (81.4)	29 (90.6)	6 (54.5)	0.008

BD = bipolar disorder; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; IQR = interquartile range; YMRS = Young Mania Rating Scale.

individuals (CGI-S = 1.6 ± 0.8 ; GAF = 78.5 ± 13.2) with BD were included. The mean age was 33.7 ± 6.8 years, 74.4% were females, 74.4% had BD-I, and 25.6% had BD-II, and the mean duration of illness was 3.7 ± 2.3 years. When a depressive episode was the first mood episode, the average time between first depressive episode and first manic/hypomanic episode was 10.4 ± 7.5 years. The mean time since diagnosis of BD, i.e., the period between the first manic or hypomanic episode and the date of the interview, was 3.7 ± 2.3 years. Altogether, 60.5% of participants had experienced psychotic symptoms during at least one mood episode. The median total number of mood episodes was 4.0 (interquartile range [IQR]: 2.0-9.0). The mean number of depressive episodes was 2.9 ± 3.1 , and the mean number of manic episodes was 3.0 ± 2.5 .

Patients experienced a mean of 1.67 ± 2.3 mood episodes between an episode of one polarity until an episode of the opposite polarity.

The clinical and demographic characteristics of participants with BD type I and type II are shown in Table 1. Compared to participants with BD-II, those with BD-I were older at onset of first mood episode ($p = 0.046$), had higher lifetime rates of psychotic symptoms ($p = 0.001$), and were more likely to report childhood trauma ($p = 0.008$), including specific modalities of trauma such as emotional abuse (0.016) and physical neglect ($p = 0.018$).

On the other hand, BD-II patients had a higher level of educational attainment ($p = 0.028$), more mood episodes ($p = 0.035$), more depressive episodes ($p = 0.024$), more mood episodes until switch to the opposite polarity ($p = 0.038$), a higher frequency of comorbid alcohol abuse ($p = 0.014$), and a higher frequency of positive family history of BD ($p = 0.008$) compared with BD-I patients.

Duration, onset pattern, and prevalence of prodromal features prior to first hypomanic/manic vs. first depressive episode

All participants reported prodromal symptoms. On average, the mania prodrome lasted 35.8 ± 68.7 months and was predominantly subacute (60.5%) or insidious (32.6%); an acute pattern (< 1 month) occurred in only 7.0% of participants. The depression prodrome lasted 16.6 ± 23.3 months on average, and was also predominantly subacute (66.6%) or insidious (29.6%); acute presentations were even more rare (3.8%).

The most prevalent specific prodromal signs and symptoms are described in Table 2. The prodromal symptoms most frequently reported prior to the first hypomanic or manic episode were mood lability (51.2%), depressive mood (48.8%), and impatience (48.8%). Those most frequently reported prior to the first depressive episode were irritability (51.8%), tiredness or lack of energy (51.8%), and depressed mood (48.1%).

Participants experienced significant differences in the frequency of specific prodromal symptoms prior to the first hypomanic/manic and depressive episode, as shown in Table 2. Compared to the prodrome of the first depressive episode, the following symptoms were more common during the hypomania/mania prodrome: mood lability

($p = 0.016$), feeling overly talkative ($p < 0.01$), physical agitation ($p = 0.02$), racing thoughts ($p < 0.01$), increased energy ($p < 0.01$), mood elevation ($p < 0.01$), being overly cheerful ($p < 0.01$), and overly self-confident ($p < 0.01$). Conversely, feeling physically slowed down ($p = 0.02$) was more common during the depressive prodrome. The duration of specific prodromal symptoms was similar during the depressive and the hypomanic/manic prodrome.

Duration and prevalence of prodromal features prior to first hypomanic/manic episode and first depressive episode in patients with BD type I vs. BD type II

The frequency and duration of prodromal symptoms to the first depressive and the first hypomanic/manic episode in patients with BD-I ($n=32$) and BD-II ($n=11$) are shown in Tables 3 and 4, respectively.

The duration of the depressive ($p = 0.080$) and hypomanic/manic ($p = 0.674$) prodromes was similar in patients with BD-I and BD-II. In patients with BD type I, the depressive prodrome lasted 9.88 ± 17.04 months and the hypomanic/manic prodrome lasted 33.26 ± 63.06 months, on average; in those with BD type II, the depressive prodrome lasted 31.87 ± 29.43 months, and the hypomanic/manic prodrome lasted 43.54 ± 86.35 months. Among specific prodromal symptoms, only suspiciousness differed significantly in terms of duration between the two groups, lasting longer in the depressive prodrome of BD-II compared to BD-I patients ($p = 0.001$).

In BD type I patients, the prodromal symptoms most frequently reported prior to the first hypomanic/manic episode were mood lability (56.3%), impatience (51.3%), and insomnia (51.3%). The prodromal symptoms most frequently reported prior to the first depressive episode were depressed mood (28.1%), irritability (28.1%), and tiredness or lack of energy (28.1%).

In BD type II patients, the prodromal symptoms most frequently reported prior to the first hypomanic/manic episode were depressed mood (54.5%) and anxiety (45.4%), whereas the prodromal symptoms most frequently reported prior to the first depressive episode were irritability (45.5%) and tiredness or lack of energy (45.5%).

The only symptom that differed between the two groups was feeling guilty or worthless, which was more frequent in the depressive prodrome of BD-II compared to BD-I ($p = 0.033$).

Duration and prevalence of prodromal features in BD patients with and without a relevant history of childhood maltreatment

In patients who experienced trauma during childhood, the mean durations of the depression prodrome and of the hypomania/mania prodrome were 15.6 ± 25.19 months and 41.47 ± 74.89 months respectively. In those who did not experience trauma during childhood, the durations of these prodromal periods were 20.16 ± 17.74 months and 11.5 ± 17.71 months respectively. The duration of the prodrome to first depressive episode was similar in these

Table 2 Frequency and duration of symptoms occurring during the prodrome to first depressive vs. first hypomanic or manic episode

Prodromal symptoms	Frequency, n (%)			Duration in months, mean (SD)		
	(Hypo)mania prodrome (n=43)	Depression prodrome (n=27)	p-value	(Hypo)mania prodrome (n=43)	Depression prodrome (n=27)	p-value
Mood lability	22 (51.2)	6 (22.2)	0.016	9.3 (18.9)	22.3 (31.8)	0.214
Depressed mood	21 (48.8)	13 (48.1)	0.955	13.9 (22.1)	11.6 (13.5)	0.739
Impatience	21 (48.8)	7 (25.9)	0.056	12.2 (22.2)	10.6 (11.5)	0.855
Overly talkative	20 (46.5)	1 (3.7)	< 0.001	7.6 (18.1)	6.0 (0.0)	0.930
Anxiety	19 (44.2)	11 (40.7)	0.776	8.5 (12.6)	5.4 (4.6)	0.434
Anhedonia	19 (44.2)	6 (22.2)	0.061	13.0 (19.6)	15.8 (27.5)	0.799
Physically agitated	19 (44.2)	5 (18.5)	0.027	8.0 (18.7)	6.5 (10.0)	0.866
Racing thoughts	19 (44.2)	2 (7.4)	< 0.001	7.9 (16.6)	3.5 (3.5)	0.747
Irritability	18 (41.9)	14 (51.8)	0.413	8.7 (13.9)	9.7 (14.1)	0.841
Increased energy or goal-directed activity	17 (39.5)	0.0 (0.0)	< 0.001	6.0 (11.1)	-	-
Decreased concentration	16 (37.2)	8 (29.6)	0.515	17.7 (38.0)	18.6 (30.8)	0.948
Tiredness or lack of energy	15 (34.9)	14 (51.8)	0.160	17.7 (24.4)	5.1 (4.8)	0.082
Weight gain or increase in appetite	15 (34.9)	6 (22.7)	0.260	22.2 (41.1)	9.0 (8.6)	0.569
Mood elevation	14 (32.6)	1 (3.7)	< 0.001	9.1 (13.4)	30.0 (0.0)	0.159
Overly cheerful	13 (30.2)	2 (7.4)	0.020	15.6 (24.6)	18.0 (16.9)	0.902
Social isolation	11 (25.3)	12 (44.4)	0.101	14.5 (20.0)	5.0 (6.3)	0.158
Decreased school or work functioning	10 (23.3)	7 (25.9)	0.799	12.4 (25.2)	14.2 (25.5)	0.882
Difficulty making decisions	10 (23.3)	5 (18.5)	0.638	25.5 (60.2)	31.4 (38.0)	0.847
Feeling worthless or guilty	9 (20.9)	6 (22.2)	0.898	11.2 (18.5)	16.0 (21.6)	0.659
Suspiciousness	9 (20.9)	4 (14.8)	0.378	8.0 (15.4)	24.7 (39.5)	0.468
Weight loss or decrease in appetite	9 (20.9)	2 (7.4)	0.118	15.1 (30.4)	3.5 (3.5)	0.620
Overly self confident	9 (20.9)	1 (3.7)	0.043	11.1 (16.5)	36.0 (0.0)	0.311
Difficulty thinking or communicating clearly	7 (16.3)	5 (18.5)	0.808	3.0 (2.3)	19.6 (36.0)	0.362
Overly creative	7 (16.3)	1 (3.7)	0.107	13.5 (18.2)	30.0 (0.0)	0.433
Defiant behavior	6 (14.0)	2 (7.4)	0.334	36.8 (60.9)	27.0 (29.6)	0.840
Inversion of the sleep/wakefulness pattern	6 (14.0)	2 (7.4)	0.334	16.0 (33.3)	13.5 (14.8)	0.922
Physically slowed down	5 (11.6)	9 (33.3)	0.027	14.4 (25.5)	5.5 (7.2)	0.488
Insomnia	5 (11.6)	6 (22.7)	0.235	16.6 (39.7)	7.3 (9.2)	0.577
Thinking about suicide	5 (11.6)	4 (14.8)	0.483	49.2 (106.6)	24.8 (13.1)	0.677
Obsessions or compulsions	5 (11.6)	0 (0.0)	0.079	69.2 (74.9)	-	-
Increased sexual energy	5 (11.6)	0 (0.0)	0.079	43.4 (65.7)	-	-
Hypersomnia	3 (7.0)	6 (22.7)	0.070	3.6 (2.0)	7.8 (8.1)	0.424
Reckless or dangerous behavior	3 (7.0)	1 (3.7)	0.498	105.3 (148.6)	1.0 (0.0)	0.725
Others	2 (4.7)	1 (3.7)	0.670	9.0 (4.2)	6.0 (0.0)	0.667
Hallucinatory experiences	2 (4.7)	0 (0.0)	0.373	7.0 (7.0)	-	-
Self-harming behavior	1 (2.3)	0 (0.0)	0.614	0.3 (0.0)	-	-
Risky sexual behavior	1 (2.3)	0 (0.0)	0.614	0.3 (0.0)	-	-
Strange or unusual ideas	1 (2.3)	0 (0.0)	0.614	2.0 (0.0)	-	-
Attempting suicide	0 (0.0)	0 (0.0)	-	-	-	-

BD = bipolar disorder; SD = standard deviation.

two groups ($p = 0.68$), while the prodrome to first hypomanic/manic episode was significantly longer ($p = 0.04$) in individuals with a history of childhood trauma.

Participants with a history of childhood maltreatment had higher rates of specific prodromal symptoms preceding the first depressive episode compared with the group who did not report these experiences (Table 5). These symptoms included social isolation ($p = 0.002$), decrease in functioning ($p = 0.03$), and anhedonia ($p = 0.05$). On the other hand, individuals who did not experience trauma during childhood were more likely to report symptoms such as excessive cheerfulness or happiness ($p = 0.04$), feeling excessive self-confidence ($p = 0.04$), and increased creativity ($p = 0.04$) preceding the first depressive episode.

Experiencing emotional neglect during childhood was associated with increased frequencies of anhedonia ($p = 0.006$) and difficulty making decisions ($p = 0.01$) during the prodrome to the first depressive episode. Conversely,

not experiencing emotional neglect was related to more frequent insomnia ($p = 0.03$) in the prodrome to the first depressive episode. Regarding the first hypomanic/manic episode, strange or unusual ideas were more common as a prodromal feature in participants who had not experienced trauma during childhood ($p = 0.034$).

Individuals who reported having experienced emotional abuse in childhood reported higher rates of oppositional behavior ($p = 0.02$) as a part of the prodrome to the first hypomanic/manic episode than did individuals with no such history. Experiencing sexual abuse during childhood was associated with an increased frequency of several specific prodromal symptoms prior to the first hypomanic/manic episode, including feeling guilty or worthless ($p = 0.004$), dangerous or reckless behavior ($p = 0.004$), suspiciousness ($p = 0.032$), and hallucinatory experiences ($p = 0.02$). Individuals who experienced physical abuse during childhood reported feeling worthless or guilty ($p = 0.007$) more often in the prodrome of the first hypomanic/

Table 3 Frequency and duration of symptoms occurring during the prodrome to first hypomanic/manic episode in patients with BD-I and BD-II

Prodromal symptoms	Frequency, n (%)			Duration in months, mean (SD)		
	BD-I (n=32)	BD-II (n=11)	p-value	BD-I (n=32)	BD-II (n=11)	p-value
Mood lability	18 (56.3)	4 (36.4)	0.255	9.6 (20.2)	8.3 (14.4)	0.910
Impatience	17 (53.1)	4 (36.4)	0.337	9.6 (20.9)	23.5 (27.6)	0.273
Insomnia	17 (53.1)	4 (36.4)	0.337	16.7 (42.6)	16.2 (29.2)	0.982
Overly talkative	17 (53.1)	3 (27.3)	0.138	8.8 (19.5)	0.9 (0.1)	0.501
Physically agitated	16 (50.0)	3 (27.3)	0.190	9.1 (20.3)	2.0 (1.0)	0.560
Depressed mood	15 (46.9)	6 (54.5)	0.661	13.6 (22.7)	14.8 (23.0)	0.914
Racing thoughts	15 (46.9)	4 (36.4)	0.545	9.8 (20.7)	0.7 (0.4)	0.403
Increased energy or goal-directed activity	15 (46.9)	2 (18.2)	0.093	6.8 (11.7)	0.5 (0.6)	0.472
Anxiety	14 (43.8)	5 (45.5)	0.922	9.5 (14.2)	5.8 (7.1)	0.583
Irritability	14 (43.8)	4 (36.4)	0.668	8.7 (14.4)	8.7 (14.1)	0.998
Decreased concentration	12 (37.5)	4 (36.4)	0.946	17.9 (41.8)	17.0 (28.7)	0.966
Tiredness or lack of energy	12 (37.5)	3 (27.3)	0.539	14.4 (24.0)	28.0 (28.3)	0.412
Mood elevation	12 (37.5)	2 (18.2)	0.238	8.1 (12.9)	15.5 (20.5)	0.495
Overly cheerful	12 (37.5)	1 (9.1)	0.077	14.5 (25.3)	30.0 (20.5)	0.568
Anhedonia	10 (31.3)	4 (36.4)	0.755	11.3 (16.5)	17.2 (28.5)	0.631
Social isolation	9 (28.1)	2 (18.2)	0.514	10.5 (14.6)	33.0 (38.1)	0.556
Decreased school or work functioning	8 (25.0)	2 (18.2)	0.644	14.1 (28.3)	5.5 (0.7)	0.691
Decreased need for sleep	8 (25.0)	3 (27.3)	0.536	8.5 (16.0)	1.3 (0.5)	0.475
Overly self confident	7 (21.9)	2 (18.2)	0.795	9.8 (16.9)	15.5 (20.5)	0.700
Feeling worthless or guilty	7 (21.9)	2 (18.2)	0.795	5.0 (3.8)	33.0 (38.1)	0.489
Suspiciousness	7 (21.9)	2 (18.2)	0.795	10.1 (17.1)	0.8 (0.3)	0.483
Weight loss or decrease in appetite	6 (18.8)	1 (9.1)	0.454	16.7 (33.0)	6.0 (0.0)	0.775
Difficulty making decisions	6 (18.8)	4 (36.4)	0.233	9.2 (19.0)	50.0 (94.9)	0.455
Difficulty thinking or communicating clearly	6 (18.8)	1 (9.1)	0.454	3.3 (2.3)	1.0 (0.0)	0.398
Inversion of the sleep/wakefulness pattern	6 (18.8)	0 (0.0)	0.122	16.0 (33.3)	-	-
Overly creative	5 (15.6)	2 (18.2)	0.843	12.6 (19.9)	16.0 (19.7)	0.847
Defiant behavior	5 (15.6)	1 (9.1)	0.590	13.0 (19.7)	156.0 (0.0)	0.003
Thinking about suicide	4 (12.5)	1 (9.1)	0.761	1.5 (0.5)	240.0 (0.0)	< 0.001
Obsessions or compulsions	4 (12.5)	1 (9.1)	0.761	41.5 (48.7)	180.0 (0.0)	0.085
Increased sexual energy	4 (12.5)	1 (9.1)	0.761	54.0 (70.8)	1.0 (0.0)	0.551
Weight gain or increase in appetite	3 (9.4)	1 (9.1)	0.978	29.3 (47.3)	1.0 (0.0)	0.656
Physically slowed down	3 (9.4)	2 (18.2)	0.432	2.0 (1.0)	33.0 (38.1)	0.456
Reckless or dangerous behavior	3 (9.4)	0 (0.0)	0.292	105.3 (148.6)	-	-
Hypersomnia	2 (6.3)	1 (9.1)	0.750	2.5 (0.7)	6.0 (0.0)	0.154
Hallucinatory experiences	2 (6.3)	0 (0.0)	0.396	7.0 (7.0)	-	-
Others	1 (3.1)	1 (9.1)	0.418	12.0 (0.0)	6.0 (0.0)	-
Self-harming behavior	1 (3.1)	0 (0.0)	0.553	0.2 (0.0)	-	-
Risky sexual behavior	1 (3.1)	0 (0.0)	0.553	0.3 (0.0)	-	-
Strange or unusual ideas	0 (0.0)	1 (9.1)	0.084	-	2.0 (0.0)	-
Attempting suicide	0 (0.0)	0 (0.0)	-	-	-	-

BD = bipolar disorder; SD = standard deviation.

manic episode, as did those who reported experiences of emotional neglect during childhood ($p = 0.03$).

Discussion

The results of this study suggest that the experience of a symptomatic prodromal period before both the first manic and the first depressive episode is very frequent among individuals with BD. Generally, the prodrome was subacute or insidious, corroborating the findings of a previous study that systematically investigated the prodromal period of individuals with early-onset BD.¹¹

This relatively long period of mild symptoms before the first mood episode and, specifically, before the first episode of mania is relevant, because it suggests a possibility of recognizing and trialing possible interventions to prevent or delay the first manic episode. Interpreted more conservatively, this finding suggests that individuals in putatively prodromal stages might at

least be protected from exposure to potentially deleterious interventions, such as administration of antidepressants or psychostimulants without mood-stabilizing agents. Sub-threshold manic symptoms and mood lability were reported significantly more frequently before the onset of the first manic episode than before the first depressive episode. This is in line with the preliminary definition of bipolar at risk (BAR) criteria proposed by Bechdolf et al.,²⁹ which include cyclothymic features and depression, subsyndromal manic symptoms or depression, and genetic risk.

This was the first study to conduct a systematic evaluation and comparison of the prodromal period in patients with BD type I and those with BD type II. The characteristics, duration, and onset pattern of prodromal symptoms were similar in the two subtypes of BD. Our observations of the signs and symptoms of patients with BD-II were similar to those reported in a previous preliminary study that evaluated 15 patients with this disorder.¹⁸ While our findings could be interpreted to

Table 4 Frequency and duration of symptoms occurring during the prodrome to first depressive episode in patients with BD-I and BD-II

Prodromal symptoms	Frequency, n (%)			Duration in months, mean (SD)		
	BD-I (n=32)	BD-II (n=11)	p-value	BD-I (n=32)	BD-II (n=11)	p-value
Irritability	9 (28.1)	5 (45.5)	0.305	5.5 (7.3)	17.4 (20.8)	0.276
Tiredness or lack of energy	9 (28.1)	5 (45.5)	0.305	3.6 (2.3)	7.8 (7.1)	0.271
Depressed mood	9 (28.1)	4 (36.4)	0.305	8.1 (9.2)	19.5 (19.8)	0.175
Social isolation	8 (25.0)	4 (36.4)	0.318	6.2 (7.4)	2.7 (2.3)	0.392
Anxiety	8 (25.0)	3 (27.3)	0.266	4.0 (2.2)	9.0 (7.9)	0.394
Physically slowed down	6 (18.8)	3 (27.3)	0.318	7.0 (8.5)	2.6 (2.8)	0.436
Impatience	6 (18.8)	1 (9.1)	0.055	7.4 (8.4)	30.0 (0.0)	0.057
Decreased school or work functioning	6 (18.8)	1 (9.1)	0.129	15.6 (27.6)	6.0 (0.0)	0.759
Insomnia	5 (15.6)	1 (9.1)	0.181	8.6 (9.7)	1.0 (0.0)	0.514
Physically agitated	5 (15.6)	0 (0.0)	0.053	6.5 (10.0)	-	-
Decreased concentration	4 (12.5)	4 (36.4)	0.139	2.6 (2.4)	34.7 (39.0)	0.198
Hypersomnia	4 (12.5)	2 (18.2)	0.318	9.7 (9.6)	4.0 (2.8)	0.475
Difficulty thinking or communicating clearly	4 (12.5)	1 (9.1)	0.239	3.5 (2.8)	84.0 (0.0)	0.000
Thinking about suicide	4 (12.5)	0 (0.0)	0.081	24.8 (33.1)	-	-
Mood lability	3 (9.4)	3 (27.3)	0.181	6.0 (0.0)	38.6 (41.6)	0.246
Anhedonia	3 (9.4)	3 (27.3)	0.181	5.0 (1.7)	26.6 (39.3)	0.394
Weight gain or increase in appetite	3 (9.4)	2 (18.2)	0.296	12.0 (10.3)	4.5 (3.5)	0.416
Suspiciousness	3 (9.4)	1 (9.1)	0.292	5.0 (1.7)	84.0 (0.0)	0.001
Feeling worthless or guilty	2 (6.3)	4 (36.4)	0.033	6.0 (0.0)	21.0 (26.1)	0.487
Difficulty making decisions	2 (6.3)	3 (27.3)	0.101	3.5 (3.5)	50.0 (39.9)	0.217
Racing thoughts	2 (6.3)	0 (0.0)	0.169	3.5 (3.5)	-	-
Inversion of the sleep/wakefulness pattern	2 (6.3)	0 (0.0)	0.169	13.5 (14.8)	-	-
Hallucinatory experiences	2 (6.3)	0 (0.0)	0.130	-	-	-
Reckless or dangerous behavior	1 (3.1)	0 (0.0)	0.235	36.0 (0.0)	-	-
Defiant behavior	1 (3.1)	1 (9.1)	0.272	6.0 (0.0)	48.0 (0.0)	-
Weight loss or decrease in appetite	1 (3.1)	1 (9.1)	0.272	1.0 (0.0)	6.0 (0.0)	-
Decreased need for sleep	1 (3.1)	1 (9.1)	0.272	1.0 (0.0)	1.0 (0.0)	-
Overly cheerful	1 (3.1)	1 (9.1)	0.272	6.0 (0.0)	30.0 (0.0)	-
Overly talkative	1 (3.1)	0 (0.0)	0.235	6.0 (0.0)	-	-
Mood elevation	0 (0.0)	1 (9.1)	0.095	-	30.0 (0.0)	-
Overly self confident	0 (0.0)	1 (9.1)	0.095	-	30.0 (0.0)	-
Overly creative	0 (0.0)	1 (9.1)	0.095	-	30.0 (0.0)	-
Others	0 (0.0)	1 (9.1)	0.095	-	6.0 (0.0)	-
Self-harming behavior	0 (0.0)	0 (0.0)	0.130	-	-	-
Risky sexual behavior	0 (0.0)	0 (0.0)	0.130	-	-	-
Strange or unusual ideas	0 (0.0)	0 (0.0)	0.130	-	-	-
Attempting suicide	0 (0.0)	0 (0.0)	0.130	-	-	-
Obsessions or compulsions	0 (0.0)	0 (0.0)	0.130	-	-	-
Increased sexual energy	0 (0.0)	0 (0.0)	0.130	-	-	-
Increased energy or goal-directed activity	0 (0.0)	0 (0.0)	0.130	-	-	-

BD = bipolar disorder; SD = standard deviation.

suggest that prodromal symptoms are not specific and showed no differences from a prognostic perspective of development of different subtypes of BD, these results are very preliminary, as the subgroups were very small and the study may have been underpowered to detect significance in numerically large differences.

In addition, we found that childhood trauma was associated with specific prodromal features prior to the first major mood episode. Previous studies that assessed the influence of this experience in BD reported that childhood trauma and maltreatment were highly prevalent and associated with triggering of bipolar manic and depressive episodes, as well as with a worse clinical course.^{23,30,31} Our data suggest that childhood maltreatment might be associated with different clinical characteristics even prior to the first major mood episode, i.e., in the prodromal phase. These differences may be explained by the influence of early stressors on the development of affective lability,²² suggesting that, in patients with a greater burden of adverse environmental

factors, the disease might be different from a more "endogenous" type. Alternatively, one may postulate that those symptoms are part of a trauma-related psychopathology and might be found in similar rates in individuals with a history of childhood maltreatment without BD. In fact, previous studies found that experiencing trauma during childhood is related to specific psychiatric symptoms.³² Therefore, the expression of psychopathology, including before the first mood episode, may be influenced by adverse childhood experiences.

Certain limitations need to be taken into account when interpreting the results of this study. Due to its retrospective design, patients had to remember symptoms that were at least moderate and that might have occurred years before the interview, and a recall bias has to be taken into account. In addition, the occurrence of depressive symptoms before the first manic/hypomanic episode could be considered both as a marker of syndromal progression and as a prodromal manifestation of BD, depending on severity. Moreover, the small sample

Table 5 Prodromal symptoms with significantly different frequencies in patients with vs. those without a history of childhood maltreatment

A. Depression prodrome			
	Any CM (n=20)	No CM (n=7)	p-value
Social isolation	12 (60.0)	0 (0.0)	0.002
Decreased school or work functioning	7 (35.0)	0 (0.0)	0.034
Overly cheerful	0 (0.0)	1 (14.2)	0.040
Overly self-confident	0 (0.0)	1 (14.2)	0.040
Overly creative	0 (0.0)	1 (14.2)	0.040
Anhedonia	6 (30.0)	0 (0.0)	0.050
	Emotional neglect (n=12)	No emotional neglect (n=15)	p-value
Anhedonia	6 (50.0)	0 (0.0)	0.006
Insomnia	0 (0.0)	6 (40.0)	0.030
B. Hypomania/mania prodrome			
	Any CM (n=35)	No CM (n=8)	p-value
Strange or unusual ideas	0 (0.0)	1 (12.5)	0.034
	Emotional abuse (n=25)	No emotional abuse (n=18)	p-value
Defiant behavior	6 (24.0)	0 (0.0)	0.025
	Physical abuse (n=13)	No physical abuse (n=30)	p-value
Feeling guilty or worthless	6 (46.1)	3 (10.0)	0.007
	Sexual abuse (n=12)	No sexual abuse (n=31)	p-value
Feeling guilty or worthless	6 (50.0)	3 (9.6)	0.004
Reckless or dangerous behavior	3 (25.0)	0 (0.0)	0.004
Suspiciousness	5 (41.6)	4 (12.9)	0.032
Hallucinatory experiences	2 (16.6)	0 (0.0)	0.020
	Emotional neglect (n=25)	No emotional neglect (n=18)	p-value
Feeling worthless or guilty	8 (32.0)	1 (5.5)	0.035

Data presented as n (%).

CM = childhood maltreatment.

The following types of childhood maltreatment did not show significant differences between groups: A) in depression prodrome: emotional abuse, physical abuse, sexual abuse, and physical neglect; B) in hypomania/mania prodrome: physical neglect.

size may limit the generalization of findings, and certainly reduced statistical power for our comparison between subgroups. As this is an exploratory analysis, we chose not to correct for multiple comparisons, as done by Zeschel et al.³³ To minimize the limitation posed by recall bias, we included only individuals who were clinically stable at the time of the study and limited the duration of illness to ≤ 9 years. In addition, we assessed prodromal symptoms using a highly detailed instrument, which made it possible to differentiate traits and personality from emerging symptoms and to evaluate the severity and interference with functioning of each of the reported prodromal symptoms. Nevertheless, this was the first study to compare the prodromes of BD type I and BD type II. The similarities between their manifestations suggest an overlap of symptomatology in the early stages of both BD subtypes, with definitive differentiation only after the first manic episode. In addition, we utilized a highly reliable instrument to evaluate the history of childhood maltreatment. Although the CTQ does not assess all types of traumatic experiences that may occur during childhood and adolescence (e.g., it does not cover exposure to violence or natural disasters), it is a valid instrument to detect different modalities of abuse and neglect which are robust markers of environmental toxicity.

In summary, this study investigated the BD prodrome using a semi-structured interview, and, to our knowledge, was the first to analyze childhood trauma and its influence on the presentation of prodromal symptoms. Our results

provide evidence of a long-lasting, symptomatic prodrome in BD and suggest an influence of clinical and environmental variables on the expression of symptoms. This should prompt increased efforts into early recognition of BD and development of low-risk preventive interventions.

Disclosure

The authors report no conflicts of interest.

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ANEXO D - Outros Artigos N° 2: Is history of suicidal behavior related to social support and quality of life in outpatients with bipolar I disorder?

Is history of suicidal behavior related to social support and quality of life in outpatients with bipolar I disorder?

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Is history of suicidal behavior related to social support and quality of life in outpatients with bipolar I disorder?

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Abstract

Background: Bipolar disorder (BD) affects the social functioning and quality of life (QoL) of its carriers, even when treated properly, and suicide continues to be a significant cause of mortality in these patients. This study aimed to investigate whether there is an association between SS, QoL and suicidal behavior in bipolar I patients compared to healthy controls.

Methods: Euthymic outpatients with BD I, both suicide attempters (SAs) and non-suicide attempters (non-SAs), were compared to healthy controls, through the Medical Outcomes Study Social Support Scale and World Health Organization's Quality of Life Instrument – Short Version.

Results: (1) No differences were noted in SS between SAs and non-SAs. Compared to healthy controls, non-SAs showed lower values in the positive social interaction domain of SS. The patients, as a whole, showed lower values in affectionate and positive social interaction domains of SS. (2) Only the environmental domain of QoL was lower in SAs than in the non-SAs. Compared to healthy controls, SAs and non-SAs had lower values in the social and psychological domains of QoL, SAs had lower values in the environmental domain of QoL, and the patients with BD, as a whole, showed lower values in environmental, social and psychological domains of QoL. (3) There was a positive correlation between SS and QoL.

Limitations: As a cross-sectional study, no causal association can be assumed.

Conclusions: Although BD is a disabling disease, patients receive inadequate SS. Interventions that may alter the SS in these patients should be investigated.

Keywords: social support; social network; affective disorder; bipolar disorder; suicide attempt; quality of life.

1. Introduction

Bipolar disorder (BD) is a chronic, recurring illness, with estimated prevalence rates of 2% if only the classic presentation of systems is considered and with estimated prevalence rates of approximately 2% if its subsyndromic forms are considered (1). There are negative impacts on the overall functioning of the patient, placing BD among the top ten causes of years lost to disability (2). Furthermore, the literature shows that BD is a potentially lethal illness. It is estimated that 25% to 50% of patients with BD will attempt suicide at least once in their lifetime and that 15%-19% will commit suicide (3, 4).

Despite the use of adequate pharmacotherapy, the course of BD is often characterized by persistent symptoms and by high rates of relapse, recurrence and hospitalizations. After the acute phase, although the individual may recover substantially, reaching a state of symptomatologic remission, the patient still presents an elevated degree of psychological suffering, cognitive dysfunction and losses in the social and work spheres with a subsequent negative impact on quality of life (QoL). The subsyndromal symptoms, especially depressive ones, may remain and thus result in a higher frequency of recurrences, with the exacerbation of symptomatology and a decrease in one's general health (5, 6). Within this context, routine inclusion of QoL assessment in clinical practice is helpful as QoL may be considered an important indicator of the level of efficiency of medical treatment (7).

Among the constructs that measure psychosocial aspects, two different, albeit related, concepts are noted: 1- structural social support (SS) and 2- functional SS. The structural SS comprises the quantitative aspect of social relationships and includes the number of people with whom the individual maintains contact or a social bond (social network) and who might or might not offer help. This type of support also involves the interconnectedness of a person's relationships and describes the existence of and relations among network members. The functional SS comprises the qualitative dimension of the relationship, referring to the resources made available to people in time of need, such as emotional, material and affective assistance. Furthermore, SS refers to the individual's perception of being valuable to the groups of which the individual is a part (8, 9, 10).

Previous studies regarding SS and BD reported that patients with BD receive less SS and that those with deficient SS have poorer symptomatic outcomes than healthy controls (11, 12, 13, 14). In addition, prospective studies confirmed that SS

has a positive influence on only the recurrence of the depressive episode (15, 16, 17, 18); another study showed the positive effect of SS only in the period of mania (19), and others affirm that the presence of SS is important in reaching remission for both states of the illness (20, 21 22). Additionally, only one study showed that SS is not an important factor in the individual's recovery (23).

Although there are favorable empirical results corroborating the position that satisfactory SS provides beneficial consequences, data concerning this topic are still scarce and methodologies vary, such as including patients in different phases of the disease and evaluating simultaneously both subtypes of BD (types I and II). Moreover, most studies have small sample sizes.

Thus, to our knowledge, this is the first study that aimed to examine whether there is an association between SS and suicidal behavior in BD I patients, evaluated only in the euthymic phase, according to strict symptomatologic criteria. In addition, we also compared the relationship between SS and QoL.

2. Methods

2.1. Participants

This cross-sectional study evaluated a convenience sample. Participants were recruited from an outpatient clinic and research center, the Mood and Anxiety Program, at a Teaching Hospital, Federal University of Bahia-Brazil.

The inclusion criteria were patients 18 years or older, diagnosed with BD I according to the Structured Clinical Interview for DSM-IV (SCID-I) (24). The patients presented in the euthymic phase as defined by scores on the Hamilton Depression Rating Scale (HAM-D) (25) and Young Mania Rating Scale (YMRS) (26) lower than seven and had not had episodes in the last two months.

The healthy control group comprised volunteers who had similar socio-demographic characteristics of the patients and did not have any axis I mental disorder diagnosed by SCID I interviewers. They were submitted to the same procedure. Two researchers (PSB, SBF) trained in these scales conducted the patients' evaluations, and two others conducted the healthy controls' evaluations (AC, NRA). If necessary, the participants were assessed in more than one instance.

Individuals who were unable to understand the study and those who refused to sign the informed consent form were excluded.

2.2. Procedure

After ensuring the remission of symptoms, the patients participated in a semi-structured interview derived from the Brazilian Research Consortium for Bipolar Disorder. Information was collected on clinical and socio-demographic characteristics and patients were interviewed with SCID-I and II (Structured Clinical Interview for mental disorders (24) and personality disorders (27), respectively). Upon completion, the participants were evaluated with the Medical Outcomes Study Social Support Scale (MOS-SSS) (8) and the World Health Organization's Quality of Life Instrument–Short Version (WHOQOL-Bref) (28).

The MOS-SSS is a brief and multidimensional questionnaire developed to assess the structure of interpersonal relationships and the interpersonal relationships' functions. This SS battery contains 5 structured SS items and 19 functional SS items that cover 4 dimensions. These functions include 1. tangible support, the provision of material aid or behavioral assistance; 2. affectionate support, physical demonstrations of love and affection; 3. emotional/informational support, empathetic understanding and the encouragement of expressions of feelings as well as relying on others who offer advice, information, guidance or feedback and 4. positive social interaction, people with whom to have fun and relax (8).

The WHOQOL-BREF is a multidimensional scale formulated to measure 4 domains: psychological, environmental, social relationships, and physical health (28).

After the assessment, the patients were divided in two groups according to the presence of previous history of suicide attempts: suicide attempters (SAs) and non-suicide attempters (non-SAs). A suicide attempt was defined as one or more self-injurious acts committed with the intent to die.

All of these instruments were validated for use in Brazilian populations. All procedures were approved by the ethical committee of this hospital and followed the guidelines of the Declaration of Helsinki/1989 and Resolution 196/96 on human research of the National Health Council. All patients and healthy controls received information regarding the research, and they were interviewed only after signing the Informed Consent Form (ICF).

2.3. Statistical analyses

The Statistical Package for Social Sciences (SPSS) software, version 18.0, was used for statistical analyses. Normality was evaluated by Kolmogorov-Smirnoff test. Quantitative variables were described as the mean values plus standard deviations or median (Md) plus interquartile range (IQR) and compared by The Mann-Whitney *U*-test or Kruskal-Wallis, for two and three groups, respectively. Absolute and relative frequencies were applied to describe qualitative variables, and Pearson's chi-square test was performed to compare them. Spearman correlation was used to correlate SS and QoL variables. A significance level of 0.05 was used for all statistical analyses.

3. Results

3.1 Sample

A total of 135 outpatients with BD I were initially selected. Three patients were excluded because they did not reach the state of euthymia during the period of assessment, and 13 patients were excluded because they had difficulty understanding and completing all of the instruments. Finally, 119 patients with BD I were assessed: 46 (38.6%) SAs and 73 (61.3%) non-SAs.

A total of 89 individuals without previous history of mental illness were invited to be interviewed to form the healthy control group, but 26 (32.6%) individuals were excluded because of the presence of at least one psychiatric disorder. Finally, 63 healthy controls were submitted to the protocol, of which 14 (22.6%) had at least one personality disorder.

The SA group had more women ($n = 31$; 67.4%), had a higher presence of axis I ($p = 0.001$) and II comorbidity ($p = 0.003$), and lower values of individual income ($p = 0.033$) than the non-SAs group. SAs and non-SAs showed lower rates of employment ($p = 0.000$) and individual income ($p = 0.019$) than healthy controls (Table 1). In the group of bipolar men, the percentage who attempted suicide was 55.5% (15/27), and in the group of bipolar women, the percentage who attempted suicide was 33.7% (31/92) ($p = 0.04$) (Table 1).

(Insert Table 1)

3.2 SS and QoL

SAs and non-SAs did not show statistical difference between any of the SS functional domains. Comparing the three groups, the positive social interaction domain was lower in non-SAs than in healthy controls ($p=0.015$) (Table 2). SAs showed lower scores in the environmental domain of QoL than non-SAs ($p=0.047$). Comparing the three groups, SAs showed lower scores in the environmental, social and psychological domains ($p=0.001$, $p=0.000$, $p=0.000$, respectively) than healthy controls. Non-SAs showed lower values in social and psychological domains than healthy controls ($p=0.000$, $p=0.000$, respectively) (Table 2).

(Insert Table 2)

The patient group as a whole had lower scores on the SS positive social interaction ($p=0.018$) and affectionate domains ($p=0.029$) than the healthy control group (Table 3).

The BD patients as a whole presented lower scores in the QoL environmental, social and psychological domains than the healthy controls ($p=0.010$, $p=0.00$, $p=0.00$, respectively) (Table 3).

(Insert Table 3)

In the structural SS, SAs had fewer close friends than healthy controls ($p=0.016$). Regarding the number of close relatives, a statistically significant difference among the three groups was not reached. We also did not find differences among the three groups in question regarding participation in sports or artistic group activities, resident meeting associations, or employee, unions, or political parties, or unpaid voluntary work in non-governmental organizations, charities, etc. (Table 4).

(Insert Table 4)

3.4- SS, QoL and suicidal behavior

A positive and significant correlation was observed among all SS domains and QoL dimensions, but the stronger correlations were found between the affectionate and positive social interaction domains of SS and environmental and social domains of QoL in all correlations ($p=0.000$) (Table 5).

(Insert Table 5)

4. Discussion

To the best of our knowledge, the present study is a pioneer research on examining the association between SS, QoL and suicidal behavior in patients with BD I, evaluated only in the euthymic state and according to rigid criteria of euthymia. The use of such restrictive inclusion criteria is intended to reduce biases in the answers, in other words, to prevent distortion in the understanding of the reality of patients in relation to their own vision of SS and QoL. Although, we did not detect that SAs had more losses in SS and QoL than non-SAs, our study confirms that patients with BD have lower SS and QoL than healthy controls.

Our data concerning the percentage of BD I SAs (39%) was in agreement with those of others studies. In fact, a systematic review revealed that 36.3% of patients with BD I reported a lifetime history of at least one suicide attempt (3), and a later study found the rate to be 40.75% (29). In addition, as described in other studies, the SAs group presented more axis I and II comorbidities (30, 31, 32) and had a higher percentage of women (29, 33, 34) than the non-SA group. Consequently, it is important to highlight that the presence of comorbidities in patients with BD is associated with poorer QoL (35).

We also found less individual income in the group of SAs and this result did not corroborate the findings of another study that showed no difference between SA and non-SA groups (33). Considering that Brazil is a country in development, with substantial economic and health problems, the possible explanation for our finding is that low income may result in an additional stressor to bipolar patients who rarely receive government financial support, thus predisposing them to suicidal behavior. Another perspective is that cognitive or other residual deficits in patients with BD may

impair their ability to obtain better paid jobs. Additionally, having a low income and possible financial problems may increase dissatisfaction with life and cause the patient to spend money on only basic needs and not on leisure, which may impair their social network and QoL (36)

As expected, the only difference in socio-demographic characteristics between patients with BD and controls were occupation and individual income, just as the diagnosis of BD negatively interferes with normal daily activities and social roles, it also affects rates of employment and productivity (13). Moreover, we tried to include controls of similar age and gender to avoid confounding interpretations of results.

4.1 SS and suicidal behavior

Several studies suggest that SS is an important factor affecting the course of BD, but the literature is still scarce on this topic. In this line of investigation, we can understand the relationship between suicidal behavior and SS in two ways: 1- SS would be more deficient in patients with suicidal behavior than in those without suicide behavior and in healthy controls because suicidal phenomena is possibly a consequence of social deprivation or insufficient SS is a consequence of their peers being unable to cope with suicidal behavior; 2- SAs would have better SS than non-SAs and healthy controls because of a reasonable perception by their family and community of the severity of the disorder.

Supporting the idea that SS is more deficient in patients with suicidal behavior than in those without suicide attempts and in healthy controls, Durkheim (1987) was the first to show that suicide varies inversely with the degree of social integration in the groups to which the individual belongs (37). Additionally, it has been found that SS, such as family cohesion or a social peer group, and parenthood may reduce the risk of suicide (30, 31, 38) and are highly modifiable factors that can be used to improve existing suicide prevention programs worldwide (30).

Indeed, some studies have been cited that living alone or without a partner is a factor associated with suicidality (39, 40). This aggravating factor is likely for individuals with BD I who have never married or are separated or divorced. This probably reflects the adverse effect that the disorder has on intimate relationships (13). Nevertheless,

like our research, there are studies that showed no difference of marital status between SAs and non-SAs (29, 33).

Another important point in our study is that SAs and non-SAs have lower numbers of close friends, a fact also reported by previous investigations. According to those studies, the social networks of patients with BD are limited in size (11, 16), and these data can be corroborated in our sample because the patients have lower rates of employment and individual income than healthy controls. In fact, being employed is usually associated with having good social relationships, as it provides enhanced opportunities for work-based social contacts (11). Additionally, some studies have showed that in patients with BD I, the likelihood of employment was significantly greater for those with higher levels of the four dimensions of SS (affectionate, emotional/informational, positive social interaction, tangible) (20, 41, 13).

In this line of investigation, SS is a complex theoretical and multidimensional construct that has been measured in several ways. It is important to highlight that the choice of using the MOS-SSS to investigate SS was due to the consideration that the structural and functional aspects of social relationships is crucial for understanding how SS affects a patient's functioning and well-being. Another reason relies on the fact that MOS-SSS was duly validated for the study population. Furthermore, the chosen scale presents a good level of reliability in monitoring SS. The only concept that is not represented in the MOS-SSS but would be relevant for investigating chronically ill populations, such as those with BD, is self-esteem, defined in terms of a positive comparison between one's self and others (8).

Comparing SAs, non-SAs and healthy controls, there is only a discrete difference in the positive social interaction domain that is greater in healthy controls ($p=0.049$). Surprisingly, in our sample, when we compared SAs with non-SAs no significant differences were found in the four SS functional domains. The negative finding concerning SS and suicidal behavior in patients with BD may be explained because our sample was too small to detect differences; or the presence of history of suicide attempts really does not interfere with the care that relatives provide in this sample of patients. In fact, cultural issues may explain our data because some studies report that social and family groups in developing countries may better support individuals with psychiatric disorders or some type of disability. Although afflicted with limited resources and health infrastructure, patients in countries like Brazil seem to have a better prognosis specifically due to their greater dependence on family

members, therefore predisposing them to a better SS and social network (42). Additionally, it is possible that patients with BD I in general may perceive their SS to be inadequate, independently of the efforts of their social groups to be supportive (9). Indeed, we have already stated that excluding the history of suicide attempts, our SA and non-SA BD I patients have similar characteristics, such as rapid cycling, history of hospitalization, marital and parental status, and polarity.

Our results also show that patients with BD as a whole perceive their SS to be more inadequate than that of healthy controls, but the differences were significant only in the affectionate and positive social interaction domains. The affectionate domain has three items: "How often is each of the following types of support available to you if you need it?: 1. someone who shows you love and affection; 2. someone who hugs you; and 3. someone to love and make you feel wanted?" So, one hypothesis is that patients with BD have lower scores in the affectionate domain because they may receive less manifestations of joy, compassion, love, awe and contentment than healthy controls, as described in another study (43).

Regarding the positive social interaction domain, MOS-SSS has 4 items such as "How often is each of the following types of support available to you if you need it?: 1. someone to have a good time with; 2. someone to get together with for relaxation; 3. someone to do things with to help you get your mind off things; and 4. someone to do something enjoyable with." The difference between patients with BD and healthy controls may be explained by the high stigma related to this disorder. In fact, stigma causes considerable negative repercussions on SS, functioning and QoL (44).

It is possible that patients with BD have difficulties in interacting with their relatives and friends because they have higher levels of "expressed emotions," a concept defined by the presence of criticism/hostility/emotion over involvement in family relationships. In fact, patients with BD seem to exhibit higher levels of self-criticism and trend toward a greater decrease in positive affect after negative feedback than healthy controls, even when controlling for mood symptoms (45). Thus, despite attempts of people around them to help, even those willing to do the best they can for those with BD, dealing with this chronic disorder is very difficult and can result in unpleasant emotions and maladaptive coping strategies among the relatives of the patients (46).

Corroborating our data, a recent review found that social relationships are significantly compromised in individuals with BD and that lower levels of perceived SS

were related to unfavorable outcomes in BD compared to those of other mood disorders and to healthy controls (47). Considering the biopsychosocial dimensions in patients with BD, SS plays a significant role in their treatment, and researchers have showed that higher levels of perceived SS lead to a better prognosis in both longitudinal (20, 21, 15, 16, 17, 18) and cross-sectional studies (11, 12, 13, 14). However, we did not find an attempt to divide SS domains in most of these studies. It is considered that evaluating dimensions of SS separately would contribute to a better understanding as to how this construct measures health and various outcomes in patients with BD.

In this sense, the hypothesis that SAs have better SS than non-SAs and healthy controls is still very difficult to justify. The cross-sectional design of some studies may not allow the affirmation of SS status at the time of suicide attempt, and other methodologies could show that better SS may be a result of the suicide attempt. Thus, to better understand this relationship, longitudinal studies are necessary to compare SA and non-SA groups with the same instruments to make prospective connections between SS and suicidal behavior. Despite the lack of evidence regarding this issue, it is reasonable to think that patients with a history of suicide attempts are a subgroup of individuals with higher severity of illness, who need to be monitored carefully by their families. In fact, to improve outcomes for patients with BD, it would be necessary to empower support providers by training them to resolve problems and conflicts, to not refuse calls of help, to express love, to help manage day-to-day life and everyday tasks and responsibilities, and to assist with financial support, a place to live or stay, personal favors and rides (48).

4.2 SS, QoL and suicidal behavior

Our study found that patients with BD as a whole perceive the social, psychological and environmental domains of QoL to be worse than healthy controls. These findings are consistent with previous studies that showed that patients with BD and a history of suicide attempt have a lower QoL (29). As BD is a progressive, chronic-course disease, which causes severe disability of the individual's global functioning, being a patient results in damage on QoL and troubles with relationships throughout

life, as shown in reviews of literature (49, 47). This impairment in QoL seems to persist even in clinically euthymic patients (50, 51, 52, 53, 54, 29)

We did not find a statistically significant difference in the physical domain of the WHOQOL-BREF, as described in another study (54). People who are affected with BD may experience frequent relapses and may not return to full function between episodes, resulting in a lowered quality of family and social life, changes in the environmental and dissatisfaction with himself and with life but not necessarily physical impairment. In fact, these patients have no physical limitations such as other diseases, so this outcome would be expected. Another relevant factor that may have influenced this result is that our patients with BD are regularly monitored in a specialized clinic for the treatment of mood disorders at a teaching hospital, which allows the prompt liaison with other specialties and ensures access to free exams and medications for various medical specialties.

Furthermore, some studies suggested that SAs showed lower QoL than non-SAs (55 29). In our sample, the SA group showed lower scores only in the environmental domain when compared with non-SAs. As well as the SS, this result may be due to a homogeneous sample.

It is noteworthy that the poorer score in two domains (affectionate and positive social interaction) of the four functional SS and lower in three (environmental, psychological and social) of the four domains of QoL, evaluated when compared to healthy controls, cannot be related to the presence of subsyndromal symptoms because we evaluated only subjects with scores lower than seven on the HAM-D scale, as discussed below. In addition, we found a positive correlation between SS and QoL, a fact that seems concordant with other studies that identify SS as a better prognostic variable. Gutiérrez-Rojas et al. (2008) found that SS may have a protective effect on mental QoL (54). Helgeson (2003) reported that the relationship between QoL and SS is linear. The stress-buffering hypothesis indicates that the relationship between SS and QoL depends on a person's level of stress. According to this hypotheses, if there is no stress or little stress, SS is unrelated to QoL (9). Therefore, as previously stated, BD is characterized by mood swings and the disease itself can be a stressor for the patient. In this sense, SS may be an important predictor of improved QoL.

4.3 Limitations and Strengths

Some limitations of the study are noted. First, this is a cross-sectional study and no causal association can be assumed. Second, we are not able to determine whether lower SS and QoL scores were already present before or after the suicide attempts, and therefore, influencing the decision to attempt suicide. Third, patients were enrolled at only one outpatient clinic, which limits the possibility to generalize our findings. Fourth, the sample size was relatively small for many of the analyses.

Despite these limitations, our study has many strengths, as it includes only outpatients with BD I evaluated during the euthymic phase, which was set under strict criteria. The importance of this lies in the fact that studies conducted on symptomatic patients are biased because one's perception is normally distorted during the presence of depressive and manic symptoms. Additionally, we used a specific and validated scale to measure SS and also studied the correlation between SS and QoL, comparing BD with and without suicidal behavior and healthy individuals. Additionally, it should be stressed that using a healthy control group may result in more reliable and real-to-life findings.

4.4 Conclusions

Although the results suggest that SS and QoL in SA and non-SA patients with BD I may not differ, the group of BD patients as a whole is deficient in SS and QoL compared to healthy controls. Additionally, a positive correlation is observed between SS and QoL that may suggest an impact of SS on QoL in this sample of patients.

In the future, the use of prospective longitudinal designs is needed to more thoroughly examine temporal associations between SS, QoL and suicidal behavior in patients with BD. Therefore, it is necessary to conduct better investigations of the social aspects that might influence symptom exacerbation and help prevent suicide attempts. Equally important is to know how SS influences the course of BD and test dimensions of SS as predictors of leading outcomes of BD evolution, which may establish causal relationships and indicate clinically relevant areas for evolution on treatment of these patients.

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Table 1: Clinical and socio-demographics characteristics of participants

Characteristics	Bipolar patients		p	Healthy Controls (n=63)	P*
	Attempters	Non-attempters			
	(n=46; 39%)	(n=73; 61%)			
Age in years†	40 (32-48)	45 (34-55)	0.099	40 (26-51)	0.054
Gender					
Male	33%	16%	0.040	29%	0.094
Have children	67%	59%	0.435	55%	0.468
Employed	20%	30%	0.201	56%	0.000
Individual Income	140(0-236)	217(0-389)	0.033	249(0-428)	0.019
Marital status					
With partner	41%	32%	0.276	43%	0.341
Years of study†	12(8-12)	12 (10-13)	0.115	12 (10-12)	0.257
Physical activity (yes)	22%	24%	0.813	36%	0.168
Length of illness	14 (6 – 24)	14 (9 – 22)	0.647	-	-
Age at BD diagnosis	30 (24 – 39)	32 (24 – 44)	0.290	-	-
Age of first episode	24 (20 – 30)	25 (18 – 34)	0.198	-	-
Polarity					
Positive	52%	55%			
Negative	34%	28%	0.766	-	-
No polarity	14%	17%			
Hospitalization	77%	70%	0.380		
Rapid cycling	20%	9%	0.076	-	-
Comorbidity Axis I	54%	25%	0.001	-	-
Comorbidity Axis II	54%	27%	0.003	23%	0.001

BD: bipolar disorder; *Comparison between the three groups; † Median (Interquartile range).

Table 2: Functional social support and quality of life among bipolar I outpatients with and without suicide attempt, and healthy controls

Domains	Bipolar Patients		P	Healthy Controls (n=63)	P*
	Attempters (n=46)	Non-attempters (n=73)			
Functional SS					
Affectionate	93.3(73,3 – 100.0)	93.3(80.0 – 100.0)	0.954	100.0(86.7 – 100.0)	0.092
Tangible	90.0(65.0 – 100.0)	90.0(65.0 – 100.0)	0.896	90.0(75.0 – 100.0)	0.982
Positive Social Interaction	82.5(63.8 – 100.0)	80.0(65.0 – 95.0)	0.521	90.0(75.0 – 100.0)	0.049^a
Emotional/ Information	85.0 (68.1 – 95.0)	80.0(67.5 – 97.5)	0.643	85.0(72.5 – 97.5)	0.661
QoL					
Physical	60.7(49.1 – 67.9)	60.7(50.0 – 71.4)	0.769	60.7(53.6 – 71.4)	0.948
Environmental	51.6(40.6 – 59.4)	56.2(45.3 – 68.7)	0.047	59.4(50.0 – 71.9)	0.005^b
Social	58.3(33.3 – 75.0)	58.3(41.6 – 75.0)	0.544	83.3(66.7 – 91.7)	0.000^c
Psychological	54.2(45.8 – 62.5)	58.3(50.0 – 66.7)	0.056	70.8(62.5 – 75.0)	0.000^d

SS: Social Support; QoL: Quality of Life. The data are expressed as median and interquartile range., *Comparison between the three groups. ^aNon-attempters vs controls p= 0.015. ^bAttempters vs controls p=0.001 ^cAttempters vs controls p=000. Non-attempters vs controls p=000. ^dAttempters vs controls p=000. Non-attempters vs controls p=000

Table 3: Functional social support and quality of life between bipolar I patients and healthy controls

Domains	Bipolar I Patients (n=119)	Healthy Controls (n=63)	p
Functional SS			
Affectionate	93.3(73.3 - 100.0)	100.0(86.7 - 100.0)	0.029
Tangible	90.0(70.0 - 100.0)	90.0(75.0 - 100.0)	0.911
Positive Social Interaction	80.0(65.0 - 100.0)	90.0(75.0 - 100.0)	0.018
Emotional / information	85.0(65.5 - 95.0)	85.0(72.5 - 97.5)	0.421
QoL			
Physical	60.7(50.0 - 71.4)	60.7(53.6 - 71.4)	0.880
Environmental	56.2(43.7 - 62.5)	59.4(50.0 - 71.9)	0.010
Social	58.3(41.7 - 75.0)	83.3(66.7 - 91.7)	0.000
Psychological	58.3(50.0 - 66.7)	70.8(62.5 - 75.0)	0.000

SS: Social Support; QoL: Quality of Life

Table 4: Structural social support among bipolar I outpatients with and without suicide attempt, and healthy controls

Structural SS	Bipolar		p	Healthy controls	P*
	Attempters	Non-attempters			
Number of close relatives	2 (1 - 4)	2 (2 - 5)	0.159	3 (2 - 5)	0.234
Number of close friends	2 (0 - 2)	2 (0 - 3)	0.477	2 (1 - 3)	0.047^a
Sports or artistic group activities ^b					
Yes ^c	34.8%	23.3%	0.173	33.3%	0.300
Resident meeting associations, employee unions or political parties ^b					
Yes ^c	19.6%	19.2%	0.958	31.7%	0.174
Unpaid voluntary work ^b					
Yes ^c	21.7%	15.1%	0.353	30.2%	0.106

SS: Social Support. *Comparison between the three groups ^aAttempters vs healthy controls p= 0.016. ^bParticipation in the last twelve months. ^cAttendance at least once a year.

Table 5: Correlation between Social Support and Quality of Life in bipolar I patients

SS / QoL	Physical	Psychological	Social	Environmental
Tangible	r= 0.182 p= 0.014	r= 0.196 p= 0.008	r= 0.274 p= 0.000	r= 0.324 p= 0.000
Affectionate	r= 0.226 p= 0.002	r= 0.333 p= 0.000	r= 0.406 p= 0.000	r= 0.363 p= 0.000
Positive Social Interaction	r= 0.261 p= 0.000	r= 0.343 p= 0.000	r= 0.424 p= 0.000	r= 0.398 p= 0.000
Emotional/Informational	r= 0.163 p= 0.028	r= 0.218 p= 0.003	r= 0.335 p= 0.000	r= 0.322 p= 0.000

SS: Social Support; QoL: Quality of Life

ANEXO E - Outros Capítulos de Livro: Comportamento Suicida e Transtorno Bipolar

Comportamento Suicida e Transtorno Bipolar

Transtorno Bipolar: teoria e clínica, 2ª edição Editora Artmed

Comportamento Suicida e Transtorno Bipolar

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Introdução

O suicídio é um grave problema de saúde pública que envolve aproximadamente um milhão de mortes por ano no mundo¹. Estima-se que, para cada suicídio consumado ocorram 10 a 40 tentativas de suicídio (TS)². A TS foi definida por Ayd, em 1995, como qualquer ato de ameaça à vida e que foi cometido com a intenção de por fim a ela. Esse tipo de comportamento engloba atitudes variadas, desde os atos mais simples de autoagressão e que não necessitam de atenção médica, até ações mais graves, nas quais a hospitalização do paciente é necessária³. Segundo a Organização Mundial de Saúde (OMS), as TS no mundo foram responsáveis por 1,4% dos prejuízos globais causados por todas as doenças e estima-se que esse índice alcance 2,4% em 2020.

O comportamento suicida (CS) é um fenômeno complexo e multidimensional que pode ser influenciado por características genéticas, sócio-demográficas, ambientais e culturais^{4,5}. Apesar desta complexidade e da necessidade da interação de múltiplas variáveis para que ele se manifeste, a presença de transtorno mental é um dos fatores mais importantes para a ocorrência deste desfecho⁶. Dentre elas, o transtorno bipolar (TB) aparece como a patologia mais associada ao suicídio e a TS⁷.

Um estudo realizado em cidades americanas que avaliou o banco de dados do Estudo de Captação de Área (ECA), feito nos Estados Unidos, com mais de 18.000 pacientes, relatou uma prevalência de uma ou mais TS ao longo da vida de 29,2% em pacientes com TB, de 15,9% em pacientes com depressão unipolar e 4,2% em portadores de outras patologias psiquiátricas do eixo I. De acordo com esse mesmo estudo, pacientes com TB possuem um risco relativo para TS duas vezes maior que pacientes com depressão unipolar e seis vezes maior que portadores de outras patologias psiquiátricas⁸.

No Brasil, um estudo epidemiológico de base populacional que avaliou 1464 indivíduos, na cidade de São Paulo, mostrou uma prevalência de TS ao longo da vida de 20,8% em pacientes com TB tipo I e 32% em portadores de TB tipo II. Em pacientes

com outros transtornos psiquiátricos, essa taxa foi de 1,1%⁹. Em outro estudo, envolvendo uma amostra de 268 portadores de TB, acompanhados em um centro especializado de atendimento, a prevalência de TS ao longo da vida foi de 41%¹⁰. Em outras amostras, 25% a 56% dos pacientes com TB reportaram pelo menos uma TS ao longo da vida e 10% a 19% morreram por suicídio^{7,11}. Além disso, em comparação com a população geral, os pacientes com TB podem ter um risco de morte por suicídio até 30 vezes maior¹².

Entretanto, apesar de o suicídio comumente apresentar-se como uma complicação das doenças mentais, a maioria dos indivíduos com transtornos psiquiátricos nunca tentou suicídio. Dessa forma, podemos inferir que pacientes que apresentam a mesma patologia com e sem história de TS podem ter características clínicas, sócio-demográficas e neurobiológicas diferentes. Para entender essa diferença, é fundamental a avaliação e a comparação das características de pacientes com e sem história de CS. Considerando o CS como resultado de uma combinação de fatores de risco individuais, eventos estressores desencadeantes e uma patologia psiquiátrica de base, a predição da TS ou do suicídio através apenas das análises estatísticas de fatores de riscos associados ao CS em pacientes com TB é falha, entretanto uma compreensão mais detalhada dos fatores de risco associados ao CS pode contribuir para redução das taxas de TS e suicídio nesta população.

Fatores de risco

Diversos fatores, incluindo características sócio-demográficas e clínicas têm sido associados ao CS em pacientes com TB. A maioria das pesquisas sugere que os fatores de risco mais fortemente associados ao CS nesta população sejam: maior número de episódios depressivos no curso da doença, idade de início precoce do TB, história prévia de TS e história familiar de suicídio^{13,14}. Alguns outros estudos, de forma menos consistente, apontam para outros fatores de risco, tais como a presença de ciclagem rápida, sintomas mistos, dentre outros. Esses resultados diversos podem ser em decorrência das várias metodologias empregadas, assim como da junção dos vários tipos de TB nas amostras avaliadas.

Pobre QV e eventos de vida estressantes foram também associados a TS em portadores de TB em alguns estudos, principalmente durante as fases depressivas da doença^{15,16}. É possível que a baixa QV seja um reflexo de baixa capacidade de

adaptação e suporte social inadequado, fatores estes que contribuiriam para um risco aumentando de TS, ou que, talvez, tendo uma baixa QV, nos seus diversos aspectos, o indivíduo se torne mais vulnerável ao processo de adoecimento¹⁶.

Em relação ao gênero, estudos indicam que em portadores de TB o gênero feminino esta associado a um maior risco de TS e o gênero masculino esteja associado a maior risco de letalidade por suicídio^{11,17}.

No que tange as características clínicas, a presença de comorbidade com transtorno por abuso de substâncias foi associada a maior risco de suicídio e outras causas não naturais de morte em pacientes com TB⁴. O abuso de álcool especificamente foi associado a maior risco de suicídio quando comparado ao uso de outras substâncias psicoativas^{17,18}. Da mesma forma, transtorno de personalidade comórbido, principalmente os do agrupamento B, assim como polaridade depressiva do primeiro episódio de humor e TB tipo II foram características clínicas associadas a um maior risco de TS¹⁹.

Existem ainda evidências que sugerem que o tempo prolongado entre o surgimento dos primeiros sintomas do TB e o início de medicação estabilizadora de humor esteja associado a um maior risco de TS, independente da presença de outros fatores associados ao CS. Em estudo conduzido pelo nosso grupo foi demonstrado que portadores de TB que iniciaram o uso de estabilizador de humor cinco anos ou mais após o início da doença, apresentaram um risco significativamente maior de TS, comparado aqueles que haviam iniciando o tratamento antes desse período¹⁰.

Existem evidências que sugerem que o temperamento ciclotímico esta associado a um maior risco de suicídio, provavelmente por apresentar reações emocionais inadequadas a eventos estressores, o que ocasiona pior evolução da doença²⁰. Alguns estudos relataram ainda que a falta de esperança é uma característica associada a maior risco de suicídio. Além disso, prejuízo funcional foi relacionado á maior risco de TS em uma amostra de pacientes com TB¹⁷.

Mais recentemente, um estudo constatou que pacientes com TB que vivem em altas altitudes podem ter maior risco de suicídio. Nestes casos, a diminuição dos níveis de serotonina e aumento da dopamina e norepinefrina associada à hipóxia em altitudes mais elevadas, podem predispor a maior irritabilidade, a alterações do humor e ao CS per se²¹.

Por outro lado, pouca atenção vem sendo dada a investigação dos possíveis fatores de proteção ao CS nos pacientes bipolares, tais como a presença de suporte social, resiliência, estilo de vida saudável, crenças, religiosidade e objeção moral ao suicídio. De fato, no estudo de Dervic e colaboradores, foi relatado que fortes objeções morais e religiosas ao suicídio estão associadas a um menor risco de CS^{22,23}. Nesse contexto, a vivência religiosa saudável pode ser uma ferramenta de enfrentamento da doença, inibindo a expressão de sintomas depressivos e melhorando a QV de pacientes com TB²⁴. Porém, ainda não está claro, se uma maior religiosidade pode exercer efeito protetor em relação ao CS nesta população, pois os resultados das pesquisas até o momento são escassos²⁵.

Assim, apesar dos muitos fatores de risco já terem sido identificados, eles não são suficientes para se prever com precisão quais pacientes bipolares irão apresentar algum tipo de CS.

Neurobiologia do comportamento suicida

Décadas de pesquisa têm demonstrado alterações na neuroquímica cerebral, envolvendo principalmente o sistema serotoninérgico, o noradrenérgico e o dopaminérgico na neurobiologia do suicídio, visto que esses sistemas são cruciais na resposta ao estresse e o seu funcionamento alterado pode ser influenciado por fatores genéticos, epigenéticos e/ou eventos de vida adversos²⁶. Além disso, anormalidades no eixo hipotálamo-pituitária-adrenal (HPA) e em outros sistemas hormonais também têm sido implicados na fisiopatologia do CS, embora esses últimos ainda derivem de um número escasso de pesquisas.

A despeito do foco na neurobiologia do CS no TB, muitas das informações disponíveis ainda derivam de estudos na depressão maior e foram reunidas nesta seção.

Neurotransmissão Serotoninérgica

Pacientes deprimidos com CS apresentaram níveis significativamente menores de ácido 5-hidroxiindolacético (5-HIAA), metabólito da serotonina, no líquor, comparados a pacientes deprimidos não suicidas ou controles^{26,27}. Baixos níveis de 5-HIAA no líquor também parecem predizer TS futuras, sobretudo as de maior letalidade, assim como o suicídio completo. Entre os vários subtipos de receptores de serotonina, vários

estudos *post-mortem* implicam o 5-HTR2A²⁶. Trabalhos recentes demonstraram expressão aumentada desse receptor no córtex pré-frontal (PFC) e no hipocampo de vítimas de suicídio quando comparada a de controles²⁸. Portanto, é provável que a suprarregulação pós-sináptica da serotonina resulte de uma resposta compensatória a uma neurotransmissão serotoninérgica reduzida^{26,27}.

.Neurotransmissão Noradrenérgica

Foram encontrados poucos neurônios noradrenérgicos nos *locus ceruleus* de suicidas com depressão unipolar, assim como aumento dos receptores β -adrenérgicos no CPF desses mesmos indivíduos. Além disso, baixos níveis urinários e plasmáticos de 3-metoxi-4-hidroxifenilglicol (MHPG), um importante metabólito da noradrenalina, foram encontrados em pacientes com CS comparados com controles. Outro estudo mostrou que a letalidade das TS em pacientes bipolares estava negativamente correlacionada com os níveis de MHPG^{26,29}.

Neurotransmissão Dopaminérgica

A neurotransmissão dopaminérgica também tem recebido crescente atenção na fisiopatologia do TB, tanto em sua fase maníaca quanto na depressiva³⁰. Essa evidência se apoia tanto na eficácia dos antipsicóticos (antagonistas dopaminérgicos) no tratamento da mania, quanto na ação dos psicoestimulantes (agonistas dopaminérgicos) na indução da mania. Além disso, o uso dos antidepressivos tricíclicos que aumentam a concentração da dopamina nas sinapses do CPF, estão mais associados a viradas maníacas que os inibidores seletivos de receptação de serotonina (ISRS) em portadores de depressão bipolar³⁰. Mais ainda, um estudo *post-mortem* demonstrou altos níveis corticais de ácido homovanílico (HVA), metabólito da dopamina, em vítimas de suicídio e homicídio comparados com aqueles encontrados nos indivíduos que morreram de uma doença, mas não vítimas de acidentes. Níveis elevados de HVA no líquor de humanos também têm sido correlacionados com agressividade²⁶.

Ademais desse embasamento farmacológico, estudos de neuroimagem estrutural e funcional também sustentam o envolvimento da dopamina no TB. A interface desse conhecimento com o CS aparece quando se verifica que polimorfismos nos receptores D2 e D3 em bipolares estão mais associados a

comorbidade com transtornos de ansiedade, a ciclagem rápida e aos estados mistos, todos eles relacionados a aumento do CS³⁰.

Eixo HPA

Com respeito ao eixo HPA, evidência considerável sugere que eventos adversos precoces na vida podem produzir mudanças duradouras na regulação da resposta ao estresse em humanos. Além disso, o eixo HPA tem relação bidirecional com os sistemas de neurotransmissores discutidos acima. Como resultado, muitos investigadores têm examinado componentes desse eixo em vítimas de suicídio. Por exemplo, um estudo *post-mortem* identificou uma diminuição significativa no número de receptores do fator de liberação de corticotropina (CRF) em suicidas comparados com controles. De forma semelhante, um aumento da imunorreatividade ao CRF foi encontrada no CPF de vítimas de suicídio. Um estudo recente também demonstrou que pacientes bipolares com uma história prévia de TS apresentavam níveis de cortisol salivar noturno 7,4% mais elevados que os controles saudáveis. Isoladamente, o TB não esteve associado a aumento de cortisol, sugerindo um papel da desregulação do estresse na mediação do alto risco de suicídio nesse transtorno de humor³¹.

Curiosamente, o teste de supressão da dexametasona (DST), uma medida usada para acessar o funcionamento do eixo HPA, mostrou que os não supressores estão mais propensos a cometer suicídio que os supressores, em estudos de décadas de seguimento. De fato, uma metanálise recente utilizando sete estudos concluiu que a não supressão no DST aumentou em 4,6 vezes o risco de suicídio. O DST também tem sido explorado como um potencial marcador biológico para depressão e, de fato, a não supressão do cortisol tem sido associada com a gravidade e pior prognóstico de episódios depressivos maiores, sugerindo que pode ser um marcador estado-dependente para o risco de suicídio. A não supressão no DST tem sido mais frequentemente encontrada na fase depressiva do TB do que em episódios de depressão unipolar²⁶.

Outros sistemas hormonais: colesterol e testosterona

A ligação entre lipídios e CS foi investigada em ensaios clínicos grandes, randomizados e confirmada através de metanálises que revelarem um aumento nas atividades relacionadas à violência, incluindo suicídio, em pacientes recebendo medicações que reduzem o colesterol. Especificamente, os estudos clínicos

sugeriram uma relação entre níveis de colesterol total reduzidos e CS. Um estudo recente mostrou níveis de colesterol e triglicérides séricos mais baixos em homens com TB que tentaram o suicídio comparados com homens bipolares sem CS²⁶.

Apoio adicional para este potencial marcador biológico vem de um estudo, no qual os parentes biológicos de portadores da síndrome de Smith-Lemli-Opitz (síndrome autossômica recessiva caracterizada por níveis anormalmente baixos de colesterol resultantes de mutações nos genes envolvidos na biossíntese de colesterol) apresentaram um número aumentado de TS e de suicídio em comparação aos controles. Os baixos níveis de colesterol têm sido associados à diminuição da atividade serotoninérgica e do colesterol cerebral, o que pode levar à redução da plasticidade sináptica e as disfunções cerebrais³².

Um estudo exploratório recente com pacientes bipolares de ambos os gêneros durante um episódio depressivo ou misto e que tinham história anterior de pelo menos uma TS demonstrou que os níveis de testosterona estiveram positivamente correlacionados tanto com o número de episódios maníacos prévios, quanto com as TS³³. É importante lembrar que, o colesterol é o precursor da testosterona e de outros hormônios, como o cortisol e o estrógeno. Apesar de a relação entre os níveis séricos de testosterona e suicídio não ser tão consistente, esse e outros andrógenos parecem estar envolvidos na fisiopatologia dos transtornos de humor e, portanto, indiretamente, no CS²⁶.

Citocinas

As citocinas são peptídeos regulatórios que participam na defesa do hospedeiro e reparo tecidual. Modulam as funções neuroendócrinas, o sono, o comportamento de doença e participam de processos neuroinflamatórios e degenerativos³⁴.

O papel das citocinas na fisiopatologia dos transtornos psiquiátricos, como o TB e o CS está sendo vigorosamente investigado. Já existem evidências de alterações imunológicas tanto no TB como no CS. De fato, em uma metanálise envolvendo pacientes bipolares foi demonstrado aumento das citocinas pró-inflamatórias e anti-inflamatórias, como as interleucinas (ITL) IL-1b, IL4, IL6, IL10, o fator de necrose tumoral (TNF)-a, sIL-2R, sIL-6R e TNFR1³⁵. Em relação aos pacientes que apresentam CS, os marcadores inflamatórios IL2, interferon gamma, IL4, IL5, IL6,

IL10, TNF- α , TGB beta1 e proteína C reativa (PCR) estão aumentados no líquido e no plasma destes. Além disso, níveis de mRNA ou expressão de proteínas de IL1B, IL4, IL13, IL6 e TNF α estão aumentados no córtex orbitofrontal de pacientes suicidas^{36,37,38}. Estes achados em comum denotam uma relação entre a disfunção imunológica no TB e no CS.

A tradução na prática clínica, porém, ainda não traz resultados promissores^{39,40,41}. Ainda como fator de confusão, temos a presença de taxas consideráveis de comorbidades clínicas nos portadores de TB, o que pode causar um viés na interpretação dos níveis das diversas citocinas. Mais estudos são necessários para avaliar diretamente o papel fisiopatológico das citocinas no CS dos pacientes com doença mental e especificamente no TB.

Genética e Epigenética

Dados de pesquisa demonstram que o CS e os transtornos de humor ocorrem simultaneamente em famílias. Entretanto, a despeito da relevância da associação entre esses dois fenômenos, a transmissão deste comportamento é apenas parcialmente dependente daquela decorrente dos transtornos de humor⁴².

Entre gêmeos, a herdabilidade estimada para o suicídio varia de 21%-50%; e de 30%-55% para TS, ideação suicida e planejamento, respectivamente. Ambos os estudos de ligação e de associação podem ser usados para identificar genes e vias relevantes associados com o suicídio. Este campo de pesquisa amplo e crescente envolve o surgimento de novas tecnologias de *microarray* e estudos de genômica funcional que podem delinear a expressão de milhares de genes e permitir estudos de genoma completo para milhares de polimorfismos de nucleotídeo único (SNPs)²⁶.

Genética

Uma revisão de estudos de associação que avaliou o CS e genes que codificam a serotonina e o seu transportador encontrou uma robusta correlação com a região promotora da serotonina (5-HTTLPR), mas não com a variante T/C 102 do 5-HTR2A. A revisão, que incluiu uma metanálise de aproximadamente 12 estudos (n=1599), mostrou uma associação significativa entre o alelo curto (S) de baixa expressão da 5-HTTLPR e o CS⁴³. Outros genes candidatos incluem a enzima triptofano hidroxilase 1 e 2 (TPH 1 e TPH 2), a catechol-O-metiltransferase (COMT) e a óxido nítrico sintetase tipos I e III (NOS I e NOS III). Uma análise recente de estudos de associação de

genoma inteiro em pacientes com TB tipo I e II mostrou que a maior associação para TS no TB foi observada em uma região sem identificação de genes (rs1466846). Enquanto cinco outros *loci* mostraram associações sugestivas. De modo geral, os resultados propuseram que o risco herdado para suicídio nos transtornos de humor é improvável de resultar de variações individuais de grande efeito²⁶.

Genes candidatos para estudos de associação em suicídio geralmente resultam de estudos neurobiológicos prévios que identificaram muitos dos sistemas descritos acima como possíveis alvos. Além disso, áreas relacionadas as neurotrofinas e aos sistemas de sinalização celular também têm sido investigados. Uma revisão recente analisou o papel de fatores de transcrição chave e genes alvo envolvidos no suicídio. Nela, a maioria dos trabalhos estudados utilizou amostras de cérebros *post-mortem* e os resultados evidenciaram anormalidades no 5-HT_{1A}, bem como variações nas proteínas G, no efetor da fosfolipase C (PLC) e nas proteínas-quinase A e C (PKA e PKC)⁴⁴. A PKC ativa o fator de transcrição da proteína ligante ao elemento de resposta da adenosina monofosfato cíclico – AMPc – (CREB) que, por sua vez, regula a expressão de genes de plasticidade neuronal, como o fator neurotrófico derivado do cérebro (BDNF). Esses resultados são corroborados com estudos que demonstram redução do CREB, do BDNF e dos receptores de quinase relacionada a tirosina (TrkB) em cérebros de vítimas de suicídio^{26,44,45}.

Epigenética

O estudo de epigenética, um ramo relativamente novo da biologia molecular, pode ampliar a compreensão da forma como o ambiente influencia a expressão gênica ao examinar mudanças fenotípicas não codificadas pelo DNA²⁶.

Mecanismos epigenéticos comuns incluem a metilação de DNA; a acetilação e a desacetilação de histonas; e a fosforilação. Um estudo recente relatou que a DNA metiltransferase (DNMT) 3b teve expressão aumentada no CPF de suicidas completos comparados com controles⁴⁶. De forma semelhante, outro estudo implicou a expressão alterada da TrkB em processos epigenéticos relacionados ao suicídio⁴⁷. Entretanto, mais conhecimento é necessário para compreender como essas alterações são mediadas e qual a sua verdadeira interferência no aumento do risco de suicídio²⁶.

Impulsividade e agressividade: endofenótipos do suicídio?

O conceito de endofenótipos suicidas candidatos também tem sido utilizado para explorar a base neurobiológica do suicídio nos diversos transtornos de humor. Pesquisadores têm definido endofenótipo como um “componente mensurável ao longo do percurso entre a doença e o genótipo distal”⁴⁸. Endofenótipos incluem construtos neurofisiológicos, bioquímicos e neuropsicológicos, nos quais a herdabilidade e a estabilidade (estado-independência) representam componentes chave de um marcador ideal. Em particular, a impulsividade e a agressividade têm sido consideradas endofenótipos candidatos associados ao CS. Outras abordagens endofenotípicas incluem o estudo do prejuízo na tomada de decisões, condutância da pele alterada e resposta a paradigmas de neuroimagem funcional. De forma geral, todos esses construtos podem ser utilizados em conjunto com outros endofenótipos já explorados no TB, incluindo regulação anormal dos ritmos circadianos, resposta a determinados “desafios” farmacológicos, déficits cognitivos (por exemplo, anormalidades de substância branca de início precoce) para melhor predizer o CS²⁶.

Com respeito aos pacientes bipolares, uma análise de regressão recente mostrou que traços agressivos ao longo da vida estavam associados com TS no passado⁴⁹. É interessante notar que estudos prévios sugeriram que o lítio pode ter fortes propriedades contra o comportamento agressivo em humanos e propriedades anti-impulsivas em modelos pré-clínicos. Notadamente, de todos os tratamentos atuais para o TB, a terapia em longo prazo com o lítio é a única associada a taxas reduzidas de CS e de mortalidade descritas em metanálises. Prováveis alvos moleculares do lítio incluem o sinal de transdução mediado pelo AMPc, ativação de CREB, aumento da expressão do BDNF, a cascata de fosfatidil-inositol, a inibição de PKC, a inibição de glicogênio sintase quinase 3 (GSK-3) e a expressão da proteína antiapoptótica 2 de linfoma de célula B (Bcl-2)²⁶.

Um trabalho complementar também tem sido realizado para desenvolver modelos animais de suicídio (por exemplo, agressão induzida por choque), a fim de testar componentes farmacológicos potencialmente protetores²⁶.

Por fim, o estudo de outras síndromes com características que contribuem para o risco suicida (impulsividade aumentada) pode suscitar outros alvos neurobiológicos. Crianças afetadas pela síndrome de Lesch-Nyhan, por exemplo, uma rara condição

hereditária caracterizada pela superprodução e acúmulo de ácido úrico, frequentemente apresentam um impulso irresistível de se machucar (mordendo ou batendo a cabeça, por exemplo). O interessante é que o alopurinol, um inibidor da xantina oxidase usado para tratar a hiperuricemia, tem se mostrado efetivo no tratamento da mania⁵⁰. A impulsividade é característica da mania, afeta a atenção e a inibição comportamental, e, frequentemente, resulta em TS. Ademais, um antagonista experimental do receptor D1 de dopamina está sendo atualmente avaliado para reduzir o comportamento automutilante de pacientes com a síndrome de Lesch-Nyhan (NCT01065558)²⁶.

Neuroimagem e comportamento suicida

A relevância da pesquisa acerca da neuroimagem no suicídio encontra respaldo na necessidade de se identificar potenciais marcadores anatômicos que sejam efetivamente úteis na predição do CS e da redução de seu risco mediante tratamento. Neste contexto, as diversas técnicas de neuroimagem podem representar uma ferramenta promissora para a elucidação de regiões do encéfalo potencialmente relacionadas à vulnerabilidade ao CS e ao desenvolvimento de estratégias públicas de prevenção de suicídio. A maioria dos trabalhos de neuroimagem e CS reuniram amostras de indivíduos com e sem história de TS com um diagnóstico em particular, com enfoque nos Transtornos do Humor, Esquizofrenia, Traumatismo Cranioencefálico, Transtorno de Personalidade *Borderline* e Epilepsia. Neles, tanto os métodos estruturais quanto funcionais foram utilizados⁵¹. No TB, particularmente, os estudos com CS ainda são escassos e com limitações metodológicas significativas, tais como englobam amostras pequenas, com pacientes em diferentes fases da doença no momento do exame, medem diferentes áreas do encéfalo avaliadas com métodos diversos de neuroimagem estrutural, assim como utilizam diferentes paradigmas de ativação nos estudos de neuroimagem funcional.

Em um estudo de morfometria baseada no voxel (Voxel-Based Morphometry-VBM), foi demonstrado que os pacientes bipolares com história de TS apresentam volumes menores de substância cinzenta nos CPF dorsolateral, orbitofrontal, cíngulo anterior, temporal superior e parietal quando comparados a bipolares sem história de TS. Mais ainda, o tratamento em longo prazo com o lítio proporcionou um aumento dos volumes destas mesmas áreas⁵². Dois trabalhos dedicados ao estudo do Corpo

Caloso (CC) mostraram que a despeito da ausência de diferenças significativas na área do CC entre mulheres bipolares não eutímicas com e sem história de TS, aquelas com história de TS e maiores índices de impulsividade mensurados pela escala de impulsividade de BARRETT (BIS-11) apresentaram menor área de joelho do CC⁵³. No outro estudo, conduzido pelo nosso grupo, que avaliou uma amostra de bipolares tipo I eutímicos, com e sem história de TS também comparados a controles saudáveis foi observado que, embora não tenha sido demonstrada diferença significativa entre as áreas do CC entre as amostras de pacientes com e sem TS, o grupo total de pacientes com TB apresentou menores volumes de istmo e de joelho do CC quando comparados aos controles saudáveis. Neste estudo, apesar da BIS-11 total e das sub escalas atenção e ausência de planejamento apresentarem maiores pontuações nos bipolares com TS quando comparados aos bipolares sem TS e ao grupo de comparação saudável, não foi observada nenhuma correlação entre quaisquer sub-regiões do CC e os escores de impulsividade⁵⁴.

Outros trabalhos sobre anormalidades da substância branca demonstraram resultados significativos: em um deles, pacientes com TB tipo I, II e com depressão unipolar com histórico de no mínimo uma TS apresentaram maior extensão de hipersinal de substância branca periventricular (mensurada pela Escala de Fazekas modificada) do que os indivíduos sem história de TS⁵⁵. De fato, uma metanálise posterior, cuja proposta foi avaliar a influência do hipersinal de substância branca em pacientes com diagnóstico de transtornos do humor com e sem TS demonstrou que os indivíduos com histórico de TS apresentavam maior extensão de hipersinal de substância branca profunda e periventricular⁵⁶. Em outro trabalho com imagem com tensor de difusão (DTI) foi verificada menor Anisotropia Fracional (medida de organização miélica e densidade axonal) na substância branca do COF esquerdo e maiores pontuações no domínio motor da BIS-11 entre os pacientes bipolares tipo I com histórico de TS comparados aos pacientes sem histórico de TS e aos voluntários saudáveis⁵⁷.

Finalmente, outro estudo conduzido em nosso meio avaliou o cerebelo de pacientes bipolares tipo I, com e sem TS, comparados a indivíduos saudáveis, por morfometria manual. Nele, a despeito dos pacientes bipolares como um grupo apresentarem menores volumes de hemisférios e de vérmis quando comparados aos

controles, nenhuma diferença significativa no volume cerebral total ou de volume cerebelar foi demonstrada entre os pacientes com e sem história de TS⁵⁸.

Dentre os estudos de neuroimagem funcional, dois estudos com tomografia por emissão de prótons (PET) sugerem anormalidades nos circuitos subcorticofrontais: em um dos trabalhos, foi utilizado um radioligante com alta especificidade para receptores serotoninérgicos e foi verificada uma maior captação no cíngulo anterior (e menor captação no mesencéfalo) entre pacientes bipolares com história TS⁵⁹; em outro estudo, pacientes com depressão unipolar e bipolar foram submetidos a PET com o ¹⁸F-fluorodeoxiglicose (FDG) como traçador radioativo e à administração de fenfluramina, a qual estimula a liberação de serotonina. O resultado deste trabalho identificou um menor metabolismo da glicose no CPF dorsolateral direito que se intensificou após a fenfluramina entre aqueles com histórico de TS⁶⁰.

Por fim, dados sobre Espectroscopia de Prótons por Ressonância Magnética em bipolares com histórico de TS são provenientes de um único estudo, no qual foi obtido o perfil espectral do COF medial de 36 pacientes bipolares eutímicos tipo I (17 com e 19 sem história de TS) e 16 indivíduos saudáveis. Como resultados, não houve diferença significativa nas mensurações dos metabólitos estudados (NAA, Cho, ml, Cr, ml/Cr, NAA/Cr); entre os pacientes bipolares com e sem TS e entre os pacientes bipolares como um grupo quando comparados aos indivíduos saudáveis. Adicionalmente, foi observada maior pontuação na BIS atencional nos pacientes com TS ($F = 4.09$, $p = 0.031$) e, como um grupo, os pacientes bipolares também mostraram maiores pontuações comparadas aos indivíduos controles na BIS total (62 ± 12.18 vs. 58 ± 9.64), na BIS atencional (18.5 ± 3.62 vs. 17.5 ± 3.68), na BIS motora (19.5 ± 5.26 vs. 18.5 ± 4.42) e na BIS ausência de planejamento (23.8 ± 5.6 vs. 22.5 ± 4.33), mas sem diferença significante. Possíveis hipóteses para justificar o encontro do perfil espectral normal incluem o uso combinado de psicofármacos com efeitos neuroprotetores e neurotróficos com maior tempo de eutímia e subsequente melhora da função metabólica, alterações metabólicas dependentes da fase da doença ou menor frequência de comorbidades psiquiátricas na amostra estudada⁶¹.

A despeito das contundentes limitações metodológicas e escassez de trabalhos em neuroimagem do CS no TB, torna-se oportuno mencionar os achados mais relevantes e contextualizá-los nos modelos vigentes de neurobiologia da regulação emocional, notadamente o proposto pelo grupo de Mary Philips: este modelo

preconiza a existência de dois sistemas neuronais: um sistema ventral, composto por estruturas subcorticais (amígdala, striatum ventral) e corticais (ínsula, cíngulo anterior ventral e córtex pré-frontal ventral) e que estaria vinculado à identificação do significado emocional de um estímulo associado à geração de estados afetivos e regulação autonômica; o sistema dorsal seria representado pelas regiões dorsais do cíngulo anterior e CPF bem como pelo hipocampo e suportariam processos cognitivos como atenção seletiva, planejamento, monitorização do desempenho e regulação voluntária dos estados emocionais⁶².

A apreciação dos resultados dos estudos de neuroimagem em pacientes com CS, em conjunto com os principais achados de estudos neuropsicológicos nesta mesma população permite corroborar a pertinência do modelo de Philips. Especificamente, alguns autores demonstraram associação entre disfunção do COF, comprometimento da tomada de decisões e CS: em um primeiro estudo, eles utilizaram o *Iowa Gambling Task* (IGT) e mostraram que os indivíduos com TS exibiam escolhas mais desvantajosas que os pacientes sem histórico de TS⁶³; em um segundo estudo, estes mesmos autores compararam indivíduos com e sem história de TS com a utilização de uma versão adaptada do IGT durante neuroimagem funcional e mostraram que pacientes com história de TS apresentavam pior desempenho na tarefa de tomada de decisões, menor ativação do COF e córtex occipital para o contraste entre escolhas vantajosas e desvantajosas e nenhuma diferença para o contraste entre ganhos e perdas, o que pode significar comprometimento da orientação do comportamento sem risco. Estes achados em conjunto sugerem que indivíduos com CS não são capazes de avaliar escolhas arriscadas de forma apropriada⁶⁴.

Ademais, anormalidades serotoninérgicas no COF descritas em um estudo *post-mortem*⁶⁵ e o encontro de menor captação de 11-C-metil-triptofano (radioligante análogo ao triptofano) no COF medial associada à letalidade do CS em estudo com PET⁶⁶ demonstram o envolvimento desta região na vulnerabilidade ao CS. A desregulação do processamento emocional que pode resultar em saliência aberrante de determinados estímulos emocionais e respostas afetivas mal adaptadas podem estar relacionadas a outras áreas descritas no modelo de Phillips, tais como o cíngulo anterior e o CPF dorsolateral. Curiosamente, estas mesmas áreas são mais ativadas em indivíduos com sofrimento emocional^{67,68}, um aspecto associado ao CS⁶⁹.

Em linhas gerais, a pesquisa da “neuroimagem do suicídio” em pacientes bipolares ainda é embrionária, mas os achados dos estudos sugerem uma base anatômica para o CS, em particular em redes neuronais frontolímbicas, cuja disfunção pode determinar comprometimento do processamento de situações de risco, tomada de decisões, resolução de problemas, perpetuação de estados emocionais negativos, prejuízo de controle inibitório, os quais podem predispor ao ato suicida.

Conclusões

O TB é uma doença psiquiátrica grave fortemente associada ao CS. Embora, tenha havido muitos avanços sobre o conhecimento da neurobiologia do TB, ele tem uma apresentação clínica variada, às vezes de difícil diagnóstico e resposta farmacológica nem sempre eficaz. Isto faz com que, o seu manejo e a prevenção do suicídio nesta população, continuem sendo um grande desafio para clínicos e pesquisadores. Estudos prospectivos são fundamentais para compreender o CS dos pacientes com TB, a fim de que possam aprimorar estratégias de avaliação, detecção e principalmente prevenção do suicídio nessa população.

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